Neurological Sciences

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5th National ANIRCEF Congress HEADACHES: PAIN AS NECESSITY

Guest Editors: V. Bonavita, G. Bussone

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Official Journal of the Italian Neurological Society

Editor in Chief **Antonio Federico**

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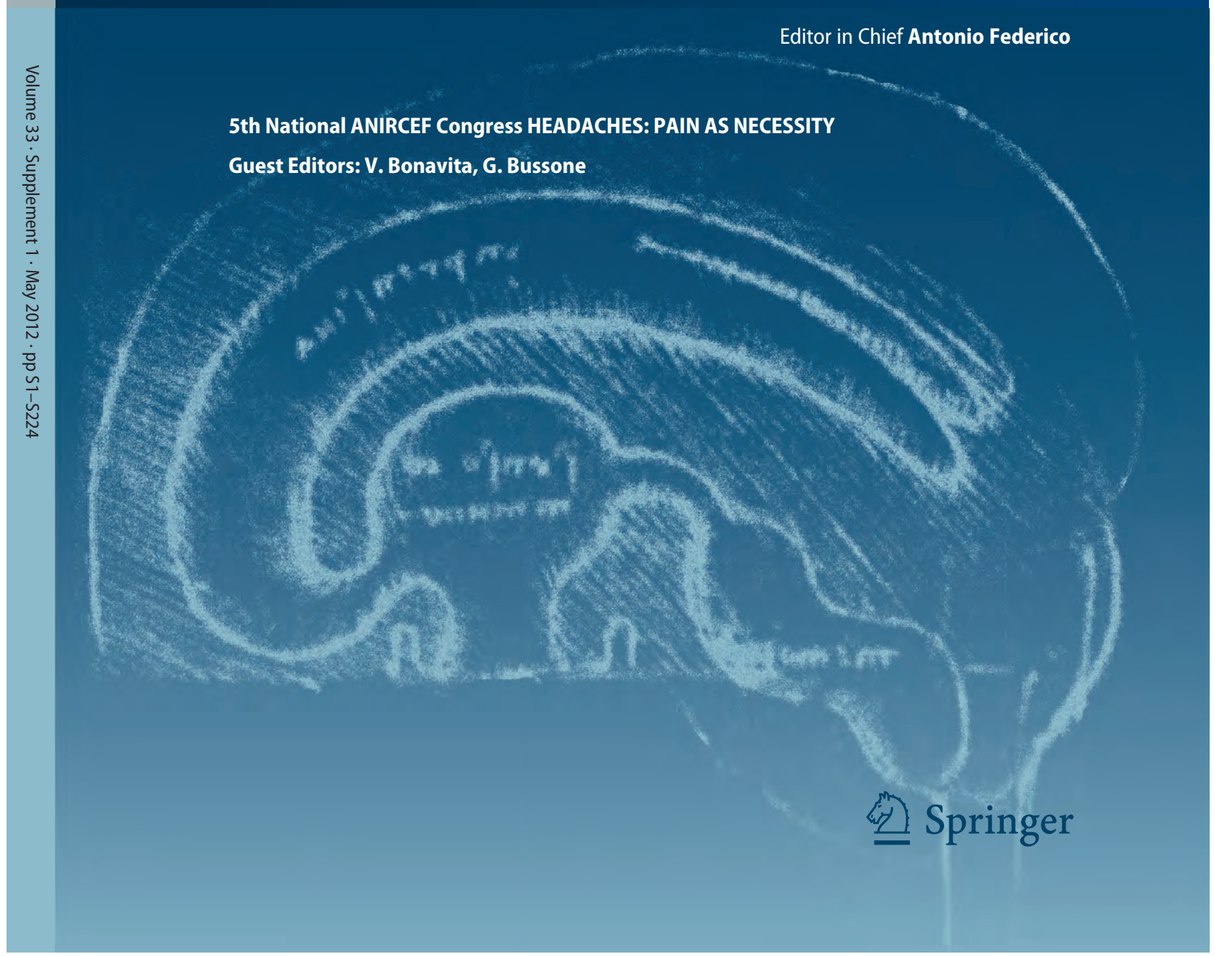

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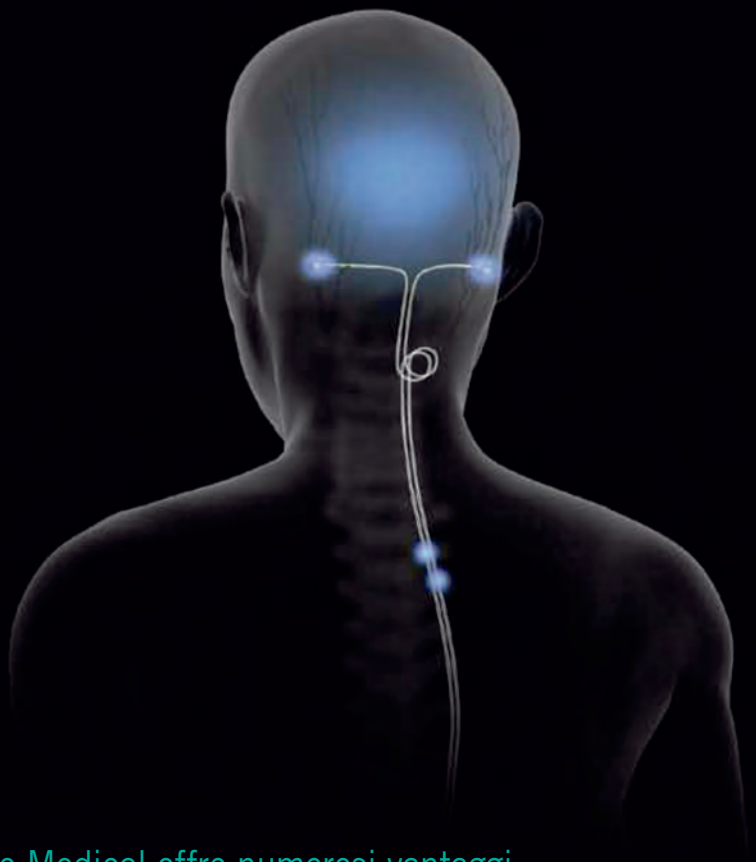

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Conflict of Interest Statement

V. Bonavita and G. Bussone declare that they have no conflict of interest related to the publication of this Supplement.

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PAIN AS NECESSITY

Pain as an evolutionary necessity

V. Bonavita · R. De Simone

Abstract The proposed title "Pain as an evolutionary necessity" could lead to a broad debate with implications covering many chapters of the medicine and particularly of clinical neurology. In the present perspective, the discussion will focus on migraine and cluster headache chosen as elective examples of biological and not only clinical conditions, that unveil the bond between pain and necessity. Migraine, cluster headache, and perhaps other primary headaches begin to be depicted in terms of recurrent activation of innate bio-behavioral specific patterns, with a crucial and highly conserved evolutionarily adaptive significance. The pan-mammalian *sickness behavior* and the *fight or flight response*, selectively activated by different kinds of pain, are here proposed as paradigmatic of migraine and cluster headache attacks associated behaviors, allowing to reformulate these forms as the inappropriate recurrent presentation of coordinated allostatic processes, modeled along million of years of natural evolution. In this light, all the multifaceted characteristics of migraine and cluster headache attacks can be reinterpreted as complex and integrated allostatic defensive reactions to an *inescapable* or to an *escapable* pain, respectively aimed to the restoration of biologic homeostasis through a temporary disengagement from active interaction with environment (migraine associated sickness behavior) or, on the contrary, to promote the coordinated biological changes preparatory to emergency and defensive behaviors (cluster headache-related fight or flight response).

This paper was presented by V. Bonavita at the "7th International Headache Seminar – Focus on headaches: update and upcoming developments – Stresa 26–28 May 2011" and published in Neurological Sciences, May 2011; Vol 32, Suppl 1:S61–66.
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PAIN AS NECESSITY

Pain stress and headache

Alberto E. Panerai

Abstract The association between pain and stress is an old one, but still it is not really clear who comes first. Pain induces stress, and stress induces pain. Pain is part of our homeostatic system and in this way is an emotion, i.e., it tells us that something is out-of-order (control), and emotion drives our behavior and one behavior is stress response. Stress comes from ourselves: the imagination we have or would like to have of us, from the image others give of us, from the goals we assume it is necessary to reach for our well-being or the goals others want us to fulfill. Stress comes from our social condition and the condition we would like, stress comes from dangerous situations we cannot control. Headache easily fits in the picture.

Keywords Pain · Stress · Headache · Emotion

Some time ago, I read an interesting and somehow enlightening paper by Montagna et al. dealing with a possible Darwinian evolutionistic view of Headache [1].

My research is not directly connected to headache, nor I have any real clinical knowledge of the disease, therefore, my understanding was limited and I probably could not fully penetrate its logic, however, it raised to me several questions that might be useful for discussing the relation between pain, stress and headache. I have to set one thing immediately: since, as I said, I am not a specialist in headache, but my research has always dealt with nociceptive or neuropathic pain, I will, and I apologize for this, speak of pain and headache as one thing.

Montagna and co-authors make several interesting points that I will use for my way through the relation between pain, stress and headache. They ask important questions: (1) is headache a symptom or a behavior? (2) may different types of pain (migraine vs. cluster headache) be assimilated to inescapable and escapable stress? (3) may migraine be compared to sickness disease and cluster headache to a fight or flight response?

Several years ago, my pain-related research was directed to the study of experimental stress, with few invasions into clinical stress, its effects on pain-responses and the underlying mechanisms (peptides and neurotransmitters). I will, therefore, look at Montagna's data staring from my experience.

I think that headache might be both a symptom and a behavior, depending on the causes. It is a symptom if it comes to the patient from a disease, it is a behavior if it comes from a reaction of the subject to an endogenous or exogenous uncomfortable "environmental" situation. Both are stress conditions, but in this picture, the difference between escapable and inescapable stresses can be that the subject can escape from a behavior, but not from a disease. As a matter of fact, I would consider both conditions as inescapable pain, since, if it is a symptom or a behavior, it physically and psychologically affects the subject who, in the actual moment of pain, has to stay with it, even if the subject will consider possible to change the behavior. I will come back on escapable and inescapable stress. Now the third question. More that the cause, i.e., escapable or inescapable stress, I would say that the difference between migraine-inescapable stress-sickness behavior and cluster headache-escapable stress-fight or flight reaction might really be looked from another point of view. Migraine is

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often a recurrent chronic disease that we can say continuously accompanies the subject who cannot escape from the condition, the subject knows it will not end, studies it and tries to understand how to live with it (this is not a passive adaptation, is an active choice!). Cluster headache is an acute episode in an otherwise well-being person, although extremely painful, but the subject knows that it has an end. Still the person can fight, not flight away, and nothing changes in relation to the disease: it remains inescapable also.

Let us go to rats. The most common stress experimental paradigms in the rat are the following: restrain (the rat is positioned for few minutes in a tube were it cannot move; short but continuous painful stresses (e.g., 3 min): these are considered inescapable stresses. Short but recurrent painful stresses (e.g., 5-s stress every 10 s for 20 min) or a 1- or 2-week stress that is articulated in a way that stress changes rotating in time: no food, wet bedding, noise, short painful stresses which are considered escapable stresses, since the animal has, between stresses, a way to "recover" and can actively try to have control (e.g., changing place).

What are the responses? In acute and inescapable stress, the animal begins fighting, tries to escape, stops and waits for the end. In the escapable stress, the animal moves around, but it does not really try to escape, it looks for a better place where to stay. Both types of stress elicit analgesia, and this is an important point. The escapable stress elicit the so called "opiate-dependent stress-induced analgesia" (the mu opiate receptor endogenous agonist beta-endorphin is involved and the antagonist naloxone can reverse it), while the inescapable stress elicits the so called "non-opiate-dependent stress-induced analgesia" that is not reversed by naloxone, but by antagonists of the kappa opiate receptor that has as an agonist the endogenous opioid dynorphin, and also involves the activation of noradrenaline and serotonin descending pathways.

Before continuing on stress models and what we can conclude from them, let me speak a few words on "sickness" behavior, since also this is a piece of Montagna's fascinating construction. Interestingly, the latter type of experimental stress (the week long one with rotating "environmental" stress) is also considered a model for sickness behavior. A "sickness" that I imagine being the one considered by Montagna—something very near to helplessness behavior, i.e., the behavior that animals show when they stop reacting since they realize that any reaction is worthless. However, there is another "sickness" behavior that is described during infective diseases or during recovery from them, a "sickness" also often referred to as non-cognitive stress. This takes origin from the high levels of cytokines present in these conditions, both peripherally and centrally, that exert their now well-known behavioral effects that go from anorexia to sleep disorders, to depression. It has been also shown the opposite: some cytokines, e.g., IL-6, may behave as primary actors not only in non-cognitive but also in cognitive stress, i.e., they are stress molecules, but still, once activated, they exert also their pro-inflammatory effects and the sensitization of pain pathways that is responsible for neuropathic pain allodynia and hyperalgesia and its maintenance.

Where are the connections to the stress, pain, headache problem? Cytokines might be the link between the animal data that show stress-induced analgesia, and the hyperalgesia that could be a player in headache.

However, there is at least another link. Stress is well known to be a determining factor in triggering the first episode of several psychiatric diseases such as depression, generalized anxiety or more often schizophrenia. Just going back for a moment to escapable and inescapable stress and the experimental stresses, it has been shown also in the human that short stress (e.g., cluster headache) elicits a strong anxiety response, while prolonged stress (e.g., migraine) elicits a milder response.

The stress involved may be a cognitive stress such as that derived from trauma and social discomfort, or non-cognitive stress such as the one derived from an infective disease. In any case, any kind of stress abnormally activates the hypothalamus pituitary adrenal axis (HPA) increasing circulating and brain steroids and decreasing the serotoninergic tone: both effects that lead to increased aggressiveness, sleep disorders, lower nociceptive thresholds, effects that might be masked in the first stress reaction, but unveiled at a later time.

But the story is even more interesting: the consequence of stress suffered in the period from the early post natal till infancy are maintained and may have long-lasting effects, more severe than a stress suffered in adulthood. This is the consequence of epigenetic changes, that get into our being and we carry with as in our life and can transfer to our descendants. This point is important. Again Montagna [2], in an exhaustive review on the genetic bases of headache, after getting to the resolution that a lot is known, but a real genetic marker has not been unveiled yet (this also holds for other diseases, e.g., psychiatric diseases) directed his attention to epigenetics. Now things get even better together: stress, but also environment.

The bad environment of a lack of parental attention, poverty, social failures, smoke or other negative situations can start epigenetic changes that end up in disease.

Two more short consideration for linking stress, pain and headache. First, we know by now that pain is one of those signals that through interoception help us to maintain our homeostasis and in a way maintain our well-being [3]. When our interoceptive messages get to the insula, and tell us that our homeostasis is in danger or already altered, the amygdala and the cingulate cortex are activated and we

experience a moment of uncertainty and instability: an emotion.

Emotion drives our behavior [4]: one behavior is stress. Stress often comes from ourselves: the imagination we have or would like to have of ourselves, from the image others give of us, from the goals we assume it is necessary to reach for our well-being or the goals others want us to fulfill. Stress comes from our social condition and the condition we would like, stress comes from dangerous situations we cannot control. Headache easily fits in the picture.

Second, let us always remember that when we speak about stress and its unwanted effects, we are really speaking of "dis-stress". Fortunately, there is also the "eu-stress": love is a eustress (should be), but a long fatiguing walk in the desert could be a eustress, if you like the desert. Jumping from bridges is a distress for most people, but a eustress for others.

Conflict of interest None.

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PAIN AS NECESSITY

Laboratory tools for assessing neuropathic pain

Giulia Di Stefano · Silvia La Cesa · Antonella Biasiotta · Caterina Leone · Alessia Pepe · Giorgio Cruccu · Andrea Truini

Abstract Neuropathic pain, i.e. pain arising as a direct consequence of a lesion or disease of the somatosensory system, affects about the 7 % of the general population. In this short review, we describe the most reliable laboratory tools for assessing neuropathic pain, such as quantitative sensory testing, laser-evoked potential recordings and skin biopsy, procedures that selectively assess nociceptive pathways.

Keywords Neuropathic pain · Nociceptive pathways · Laser-evoked potentials · Skin biopsy · Quantitative sensory testing

Introduction

According to the latest definition, the term neuropathic pain refers to pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [1].

Neuropathic pain affects the 7 % of the general population [2] and often causes a severe disability.

As clinical and experimental studies demonstrated that neuropathic pain arises as a consequence of nociceptive pathway damage, the assessment of the nociceptive pathway function plays a crucial role in the management of patients with neuropathic pain. Laboratory tests for assessing neuropathic pain measure an objective response and thus they can quantify the damage to the nociceptive afferent pathways.

This short review summarizes the most reliable laboratory tools for assessing neuropathic pain in human patients.

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Quantitative sensory testing (QST)

Quantitative sensory testing is a psychophysiological measure of perception in response to mechanical, thermal and painful stimuli of controlled intensity [3, 4]. For each kind of sensation, the perceptive threshold is determined by applying stimuli to the skin in an ascending and descending order of magnitude. Mechanical sensitivity for tactile stimuli is measured with plastic filaments that produce graded pressures, such as the von Frey hairs, pinprick sensation with weighted needles, and vibration sensitivity with an electronic vibrameter. Thermal perception and thermal pain are measured using a thermode, or other device that operates on the thermoelectric effect [3, 4].

QST has been used for the early diagnosis and follow-up of small-fibre neuropathy that cannot be assessed by standard nerve conduction study, and has proved useful in the early diagnosis of diabetic neuropathy [3, 4]. QST is also especially suitable for quantifying mechanical and thermal allodynia and hyperalgesia in painful neuropathic syndromes, and has been used in pharmacological trials to assess treatment efficacy on provoked pains [3, 4].

QST abnormalities, however, cannot provide conclusive evidence of neuropathic pain, because QST shows changes also in non-neuropathic pain states, such as rheumatoid arthritis and inflammatory arthromyalgias [3, 4].

Laser-evoked potentials

Standard neurophysiological responses to electrical stimuli, such as nerve conduction studies and somatosensory-evoked potentials, are useful to demonstrate, locate and quantify damage along the peripheral and central pathways, but they do not assess the function of nociceptive pathways

[5]. According to the EFNS guidelines on neuropathic pain assessment [5] and the Recommendations of the International Federation of Clinical Neurophysiology [6], LEPs are the easiest and most reliable neurophysiological technique for assessing nociceptive pathway function.

Laser-generated radiant heat pulses selectively excite free nerve endings in the superficial skin layers and activate Aδ and C nociceptors [7]. LEPs consist of a lateralised component (N1), generated in the SII area and in the insular cortex bilaterally, and a vertex potential consisting of a N2–P2 complex. Whereas the N2-LEP component is believed to reflect neuronal activity in insular networks and possibly the anterior cingulate cortex, the P2-LEP originates from the anterior cingulated cortex alone [8, 9].

LEPs have proved reliable for assessing damage to the peripheral and central nociceptive system in peripheral neuropathies, syringomyelia, multiple sclerosis, Wallenberg syndrome and brain infarction [10, 11]. In peripheral and central neuropathic pains, LEPs are more sensitive than any other neurophysiological test and the finding of LEP suppression helps to diagnose neuropathic pain [5].

The trigeminal territory is particularly advantageous for laser-evoked potential (LEP) recording because of the short conduction distance and high receptor density. Trigeminal LEPs are of higher amplitude and are recorded more easily than LEPs after limb stimulation. Trigeminal LEPs have been studied in classical and symptomatic trigeminal neuralgia, trigeminal sensory neuropathy, Postherpetic neuralgia, temporomandibular disorders, and headache [12–14]. In general, in conditions that engender structural damage, such as herpes zoster, compression by tumours, or multiple sclerosis, LEPs are abnormal. In temporomandibular disorders, tension-type headache, or migraine, the LEP latency—though other types of abnormalities may be found—is always normal.

Skin biopsy

Skin biopsy is a safe and reliable tool for investigating nociceptive fibres in human epidermis and dermis [15]. Skin biopsy can be done at any site of the body, with a disposable punch, using a sterile technique, and under local anaesthesia.

Punch biopsy produces a sample of skin that includes the epidermis and the superficial dermis. Immunostaining of 50 μm thick sections labels the different structures (e.g., nerve fibres, sweat glands, blood vessels, and resident or infiltrating cells). The most commonly used marker for nerve fibres are antibodies against protein gene product (PGP) 9.5, a form of ubiquitin carboxyl-terminal hydrolase [15]. PGP 9.5 is widely distributed in the peripheral nervous system and is a non-specific panaxonal marker.

The two commonly used immunostaining methods for investigating cutaneous innervation are bright-field immunohistochemistry and indirect immunofluorescence with or without confocal microscopy [16]. Only the bright-field microscopy method has been used to establish normative reference ranges and diagnostic performance [15].

Many investigators have used skin biopsy to investigate epidermal nerve fibres in various peripheral nerve diseases, such as diabetic neuropathy [17], infectious and inflammatory neuropathies [18]. In all studies, epidermal nerve fibre density was significantly lower in patients with neuropathy than in controls.

Although skin biopsy selectively assesses ENF density and correctly diagnoses small-fibre neuropathy, no studies have reported a direct relationship between neuropathic pain and skin biopsy data. In other words, whereas examination of a skin biopsy invariably discloses reduced ENF density in patients with painful neuropathy it occasionally does so also in patients with non-painful neuropathy.

Conclusions

Laboratory tools for assessing neuropathic pain have advanced enormously over recent years. They help in diagnosing neuropathic pain and quantifying damage to the nociceptive pathways, thus representing an extremely useful support to clinical examination.

Conflict of interest The authors have no conflict of interest to declare.

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PAIN AS NECESSITY

Allodynia and migraine

Marco Aguggia

Abstract An impaired processing of sensory afferents in the brainstem plays a key role in the development of migraine attack and for many of its clinical aspects. The repetition or prolonged of painful stimuli over time would be able to produce a prolonged and reversible increase of excitability and synaptic efficacy in the nociceptive pathways of the central nervous system. This phenomenon, known as sensitization, involves specifically the caudal trigeminal nucleus. Being an aspect of untreated migraine, allodynia is more common in patients with chronic migraine and migraine with aura, often associated with motor and sensory symptoms sometimes present during the attacks. The presence of allodynia in the course of migraine attack greatly increases the disability of the patient and its recognition, as well as from a therapeutic point of view, it is essential in the management of migraine patients.

Keywords Migraine · Sensitization · Cutaneous allodynia

Introduction

Migraine is a neurological disorder characterized by recurrent attacks of headache, most often unilateral with throbbing pain, associated with nausea and/or vomiting, phono and photophobia, feeling of tiredness and irritability. In the course of migraine attack, is frequently found an increased responsiveness to stimulation usually not able to cause pain and innocuous activity, which may become painful. The perception of pain in response to non-nociceptive stimuli is usually called allodynia. Over the decades, the theories regarding the pathophysiology of migraine attack have evolved, ranging from a purely vascular hypothesis to a more complex interpretation that places the central dysfunction as a key role. A pathogenetic paradigm also provides neurotransmitter, genetical and biological aspects which support the current theories on migraine pathogenesis [1]. The allodynia in migraine patients may well represent the clinical correlate of central sensitization [2, 3].

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Concept of sensitization

It is believed that the central sensitization should be considered as a physiological response underlying allodynia in migraine patients. In the late 90s, in animal models, there have been the first reports related to the central sensitization after nociceptive stimulus. They were obtained using a nociceptive inflammatory soup, consisting of histamine, serotonin, bradykinin, and prostaglandins, applied to the dura mater [4]. This caused sensitization of the second-order neurons of trigeminal nucleus and dorsal horn, as a result of converging nociceptive stimuli applied at meningeal and cranio-facial levels [5]. In practice, at the base of migraine pain and allodynia there are peripheral and central neurons of the trigeminovascular system, located in the trigeminal ganglion of Gasser and in the dorsal horn of the spinal cord. The sensitization, by reducing the activation threshold and increasing the responsiveness of these neural structures, expands the receptive fields of second-order neurons. In this way, the development of throbbing pain during migraine attacks could be related to a sensitization of meningeal neurons, and the allodynic phenomenon seems due to sensitization of central trigeminovascular

neurons on which converge the meningeal sensory inputs and cranio-facial skin sensory perceptions [2, 6]. Subsequent to the painful phase, the trigeminovascular activated neurons become responsive to changes in intracranial pressure produced by the arterial pulse, thus generating the throbbing pain classically perceived during migraine attacks and make migraine patients hyper-responsive to stimuli normally harmless.

Allodynia

Through an alteration of chemical functions and an different response to drug therapies, the central sensitization occurs with the cutaneous allodynia. This is defined as the perception of pain in response to sensory stimuli of various kinds, not able to generate pain in normal conditions. The second-order neurons in the caudal trigeminal nucleus, or third-order thalamic neurons are involved in the genesis of central sensitization, and allodynia determines the final clinical symptoms [2]. Using specific sensitivity tests and questionnaires, the development of allodynia during a migraine attack is around a percentage close to 80 % of the entire migraine population [7–9]. In particular, in a population study, Lipton et al. [10] stated the prevalence of allodynia in migraineurs was 63.2 %, reaching aspects of severity in about one-third of patients. Moreover, the allodynia itself was more common among women (74 %) than men (57 %). In order to determine the presence of allodynia in the course of migraine attack, specific tools are used for the quantification of the pain threshold to thermal and mechanical stimuli applied to the skin (quantitative sensory testing, QST). Validated questionnaires have demonstrated a good reliability for the determination of allodynia both in critical and intercritical periods [7]. There are evidences of a direct and increasing correlation between allodynia and aura, and duration of illness [10, 11]. An inverse relationship would instead be present between allodynia and aging [10]. As part of the cephalic chronic pain, Bigal et al. found that as many as 68.3 % of patients with transformed migraine presents allodynia, compared with 62.2 % of those with episodic migraine. Also, just in patients with transformed migraine allodynia assumed characteristics of greater severity [12].

Studies on allodynia

Burnstein et al. [2, 3] initially observed that cutaneous allodynia develops in 79 % of patients during migraine attacks. These findings were later confirmed in several studies [9, 13–16]. The allodynia should be considered as an important aspect of untreated migraine attack in a considerable proportion of patients with episodic migraine, assuming predominant aspect in chronic migraine. It is not yet clear what allodynia contributes to the genesis of pain and disability during migraine attacks, but it is sufficiently demonstrated its correlation with the severity of the attack and some aspects such as aura, motor and vegetative symptoms. At the same time the development of allodynia is associated with the development of resistance to treatment, especially the triptans. Currently it is not clear as to whether the refractoriness to treatment is attributable to an increase in the severity of the attacks, or whether the development of a condition of allodynia may be the primary cause of a loss in effectiveness of the treatments used in the time [10, 17].

Allodynia and comorbidity

There are several reports about the association between allodynia and migraine features. The cutaneous allodynia correlates not only with disease duration, attack frequency and disability, but also with aura, brain lateralization of pain, presence of nausea/vomiting during attacks, phonophotophobia. A relationship was also found major depression and obesity [10].

Conclusions

The allodynia is a frequent and important feature in the migraine population, able to influence the severity of the attacks and their tendency to become chronic. In migraine patients, it is reasonable to hypothesize that allodynia, produced by processes of sensitization, can be an expression of an alteration of the nociceptive control, thus favoring the migraine chronification. Obviously other factors, such as psychiatric comorbidity, may play a key role in this process [18]. The final result would lead to a reduction of the control mechanisms of pain and to the loss of efficacy of therapies. An early treatment of migraine patient must be considered the best strategy in preventing the appearance of allodynia, or, at least, reduce the risk of migraine chronification [19]. Further studies are needed to clarify if allodynia should be real-modifiable risk factor in the progression of migraine.

Conflict of interest The author certifies that there is no actual or potential conflict of interest in relation to this article.

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New prospects in the taxonomic classification of primary headaches

G. C. Manzoni · P. Torelli

Abstract In the field of primary headaches, we have a very useful classification tool for the clinical characterization of individual attacks, but we lack a classification tool for the characterization of primary headache patients. Just because the reasons for this lack have been partially overcome by the knowledge that has been gained in the meantime and because clinicians and researchers are increasingly pressed to find new and reliable ways to manage certain primary headache forms, including so-called chronic migraine, we now have an imperative commitment to provide a syndrome classification.

Keywords Primary headache · Headache · Classification · Headache classification · Chronic headache

Introduction

All processes of mental ordering, communication and implementation of any activity require the preliminary structuring of classification systems that are extensively pondered and agreed upon. This requirement is all the more necessary when dealing with scientific disciplines for purposes of study and research.

Thus, in the field of medicine as well, the availability of a nosological classification system has always been considered the first and foremost step for an adequate and feasible approach to the different disorders. Headaches are certainly not the exception to this general rule. On the contrary, so-called primary headaches are an archetypal example of such assumption. As, by definition, these headaches have no known organic substrate, they all the more need a taxonomic classification that will allow investigators to approach them with a correct methodology.

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Early attempts at headache systematization

There are many ways to organize a classification system. The first attempts at headache systematization were made in the eighteenth century, when Boissier de Sauvage [1], following the example of other contemporary systematizations in the field of natural sciences, worked out a classification that was basically a cataloging of individual cases and therefore turned out to be as detailed as it was fragmentary.

Much more recently, after the success encountered among headache scientists by the diagnostic criteria proposed by Vahlquist [2] in the 50s', the classification of the Ad Hoc Committee on Classification of Headache [3] was widely used by researchers in the two decades between the late 60's and the late 80's. This classification was based on purely aetiological criteria and used terms such as "vascular headache" or "muscle-contraction headache" to define the different types of primary headache. Of course, as investigators were refining their knowledge, this terminology soon became obsolete and no longer acceptable. In addition, the classification of the Ad Hoc Committee on Classification of Headache was merely a list of the different types of primary and secondary headaches, providing a somewhat vague description for each one of them.

Given the objective difficulty—or rather the sinful presumption—of basing a primary-headache classification on aetiological criteria, around the mid-80's a clinical

subdivision of primary headaches was proposed which distinguished between episodic and chronic types based on the temporal pattern of attacks (chronobiological classification) [4]. This was an attempt that had a limited spread and length of utilization, but nonetheless paved the way for the introduction of current international classifications based on purely clinical criteria.

Modern headache classifications

Thus, in those same years, as it became clear that a new classification tool was imperatively needed, a broad committee of international experts was charged with providing a classification of headaches that could meet the following requirements: (a) to tidy up the complicated jumble of disparate terms used until then to define individual headache types; (b) to use purely clinical, not etiopathogenetic terms; (c) to systematize the different types of primary and secondary headaches, according to a hierarchical order of increasing diagnostic sophistication; and (d) to work out accurate, essential clinical criteria indispensable for a diagnostic formulation of each recognized headache type. The committee's efforts led, in 1988, to the International Headache Society (IHS) classification of headache disorders, cranial neuralgias and facial pain [5], which soon became widely used by both researchers and clinicians.

Indeed, the merits of the 1988 IHS classification are so great that there can be no doubt about the role it played all over the world in significantly improving headache knowledge on the one hand and in ensuring a more correct and adequate patient management on the other. More generally, it represents a fully adequate tool that provides a reliable approach to a very complex field of medicine and as such it has greatly contributed to making a still misunderstood chapter worthy of scientific consideration.

In 2004, thanks to the new knowledge gained in the meantime, the IHS made a number of changes, additions and adjustments, which led to the second edition of the International Classification of Headache Disorders (ICHD-II) [6].

ICHD-II limitations

Luckily, we now have an international classification of headache disorders that we can reliably use in clinical practice. However, alongside its already mentioned and unquestionable merits, this classification, too, has some limitations that are becoming increasingly apparent over the years. I am certainly not talking about individual issues that can easily be solved, especially after the publication of the 2004 edition, e.g., a better definition of NDPH, a more adequate placement of hemicrania continua, and so on—I could give countless examples of other issues that will certainly be tackled by the next edition (ICHD-III) planned for early 2013 [7]. Incidentally, this demonstrates that the ICHD-II is a dynamic, not a static tool, which fortunately needs frequent updating to keep abreast of the relentless evolution of knowledge.

The ICHD-II's true limitation is not in its details, but in its substance. This limitation is the logical consequence of the same basic principles the ICHD-II has been structured on.

In the introduction to its 2004 edition [6], Olesen stated that "Classification and diagnostic criteria can be aetiological or descriptive and the latter can be syndromic or symptom-based. Both first and second editions of *The International Classification of Headache Disorders* are aetiological for the secondary headaches and symptom-based for the primary headaches. The fact is that the evolution of primary headache syndromes cannot be predicted. The evolutionary history cannot be classified until much bigger and better studies of the evolution of migraine patients become available. Like the first, this second edition of *The International Classification of Headache Disorders* classifies patients according to the phenomenology of their headache(s)".

So much effort went into sticking to this preliminary stance that we saw, for example, the otherwise incomprehensible disappearance of the fourth-digit diagnostic level for cluster headache in the passage from the first IHS edition [5] to the second ICHD-II edition [6]. This was the level that distinguished between chronic headache types based on whether the chronic pattern had been there since onset or it had been acquired over the years after a typical periodic start.

Consistent with the original assumption—parts of which we can all agree on—the classification editors managed to work out a very useful, though still perfect, tool. However, it is not true that this tool enables a classification of patients. Rather, it works very well in classifying attacks in the different types of primary headache; better still, it can be used to classify individual attacks; more precisely, it provides a snapshot of a particular precise moment in a single attack.

Thus, for many years we have been able to use a tool that proved indispensable for some types of research, primarily trials of symptomatic drugs such as triptans (which were introduced in those same years), but also studies aimed at investigating the underlying pathogenetic mechanisms of pain or aura. This tool also proved highly useful in clinical research to better define the phenomenology of the attacks characterizing the different headache types and has become a reference in clinical practice as well, favouring remote communication between physicians.

On the other hand, first the IHS [5] and later the ICHD-II [6] proved only partially suitable for epidemiological research. Although formally correct, its strict methodological application in this field translated into a huge amount of figures and percentages, which still today may not be appropriately interpreted. Indeed, if the tool I'm using is designed to measure attacks, I can not say that I used it to measure patients. In other words, if I apply the ICHD-II criteria and find that 10 % of the general population has had at least one attack of migraine without aura in the past year, I'm not entitled to claim that 10 % of the population "suffers from" migraine without aura. Yet, today, this is precisely the deceiving message that continues to be heard, because we forget that the ICHD-II, as clearly stated by Olesen, is not a classification of syndromes. I want to say it once again: it is an excellent classification of precise moments occurring within individual attacks.

Current issues in the nosological systematization of primary headaches

We can easily understand what we can or cannot, in spite of all our efforts, reasonably diagnose using the ICHD-II when we try to use it ignoring its working modes, i.e., the basic principles on which it is structured. An obvious example of what the ICHD-II cannot do, because of the very nature of its structuring prevents if from doing it, is the study of the chapter about chronic daily headache. This is something that all those concerned with the study of this highly complex and interesting primary headache type soon realized. In no other headache type does one have to pay attention not so much to individual episodes as to patients as a whole, considering their entire histories preceding observation and all their current physical, psychic (e.g., presence of different and very frequent comorbidities) and pharmacological (e.g., very probable overuse of symptomatic drugs) aspects.

As we saw before, in the introduction to the ICHD-II of 2004 [6] Olesen stated that there is too little knowledge of primary headaches to allow a syndromic classification. It is true to say, though, that a careful review of the ICHD-II shows a few instances that appear to contradict this assumption. This is the case, for example, of the introduction of NDPH, which is essentially—and very arbitrarily—differentiated from chronic tension-type headache, based less on a different clinical phenomenology than on presumed differences in the time-related course of the disease. Apart from that, today, 8 years later, we believe that we need to make some considerations resulting from clinical experience and taking into account the urgent and no longer delayable needs of headache researchers. Let's try to summarize these considerations: (a) It is true that clinical features characterizing patients (not only attacks) with primary headache have been known and unquestionable for many years now, e.g. the patient's family history, age at onset and the different comorbidities in migraine, migraine improvement during pregnancy, the patient's non-healthy habits in cluster headache, etc. (b) In the years that have passed since the ICHD-II of 2004, several studies have been published in the literature that shed some light on the natural history of primary headaches and on predictors for their evolution. (c) Specialized research into the field of so-called "chronic" primary headache is being heavily affected by the lack of an adequate methodological tool for their classification, which entails a great risk of conducting studies that will not yield reliable and comparable results and of preventing drug trials from being performed because of difficulties in homogeneous patient recruitment. Efforts have certainly been made to better describe patients with so-called chronic headache, or chronic migraine, and some revisions [8] or proposals of revision [9] of the ICHD-II to that effect have been advanced, but their usefulness is limited to certain aspects of the issue. (d) Also the IHS classification of 1988 [5], and this was one of its greatest merits, started from very few certainties in the literature (some validations were made only after its publication) and was essentially based on the consensus of experts. (e) Would not this be the right time to try to develop a classification also for primary headache patients?

Conclusion

Olesen's reflections in the introduction to the ICHD-II [6], which I reported and commented on above, were something we could agree on at the time. But, in light of current knowledge and needs, they appear no longer enough to keep us from making what in our opinion is maybe a far-fetched but long-overdue attempt at classifying primary headache patients.

Clearly, there is not an attempt aimed at developing an alternative to the ICHD-II. The ICHD-II is a classification that, with the obvious and already planned adjustments [7] will continue to play an increasingly crucial role as a reference for clinicians and researchers whenever they need a useful tool for the characterization of primary headache attacks. This is really about thinking of a complementary classification to the ICHD-II. To the question "What do we want to classify?", the ICHD-II has always been and is ever more able to reply: "primary headache attacks". Well, now the time has come to supplement this classification with another one, that to the question: "Whom do we want to classify?", will be able to reply "primary headache patients".

This is undoubtedly a complex and challenging operation, which will need constant updating, as it had happened and is still happening with the classification of psychiatric disorders [10]—a classification with starting methodological points similar in many respects to those that need to be tackled in a classification of primary headache patients. But this is also a necessary, no longer delayable operation: we should find in ourselves the same enthusiasm and the courage of those people who around the mid-80's developed the first IHS classification [5].

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

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A redefinition of primary headache: chronic migraine

P. Torelli · G. C. Manzoni

Abstract In the field of so-called chronic daily headache, it is not easy for migraine that worsens progressively until it becomes daily or almost daily to find a precise and universally recognized place within the current international headache classification systems. A proposal is advanced to differentiate between a form of high-frequency migraine without aura (10–20 days of headache per month for at least 3 months), to be considered as a migraine without aura subtype, and a form of transformed migraine (TM), to be considered as a complication of migraine. TM—a name that should be preferred to chronic migraine (CM)—would then replace the latter, from which it would distinguish itself by the more restrictive diagnostic criteria (at least 20 days of headache per month for at least 1 year, with no more than 5 consecutive days free of symptoms; same clinical features of migraine without aura for at least 10 of those 20 days).

Keywords Chronic migraine · Transformed migraine · Chronic daily headache · Chronic headache · Migraine

Introduction

In the last three decades, a fiery debate has been raging about chronic daily headache (CDH) in general and about chronic migraine (CM) and medication overuse headache (MOH) in particular. To sum up the question in a few words, we can say that the issue revolved around two antithetic views [1–3].

On the one hand, there were those who thought that CDH was a group that naturally included different subtypes, but was nonetheless autonomous and therefore should be considered, assessed and classified independently of the other primary headache forms [3–5].

On the other hand, there were those who thought that CDH was nothing but an entirely generic definition, a non-diagnosis or a diagnosis still waiting to be defined [6, 7].

The former view was more closely related to clinical practice, the latter view paid more attention to formal aspects.

Milestones in the classification of CDH and CM

Mathew et al. [2] in 1982 were the first to call attention to the possibility that migraine may be transformed into daily headache over time.

Five years later, the same group of researchers [3] subdivided CDH into three different groups: "Type I starts as daily or near-daily headache with no change in the severity and lacks migrainous features; Type II starts as daily or near-daily headaches with occasional more severe headache with some migrainous features; Type III (transformed or evolutive migraine) starts as a clear-cut occasional episodic migraine … with increasing frequency over the next many years … evolving into chronic daily headaches." These authors in 1987 were not yet talking about chronic tension-type headache (CTTH), nor about new daily persistent headache (NDPH) [8]. Both were still unknown definitions, even though the two first CDH types

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could seemingly be identified with these two headache forms. Mathew himself [9] in 1993 definitely chose the name "transformed migraine" (TM), which he included in the first true CDH classification, alongside CTTH and NDPH.

The following year, Silberstein, together with Lipton, Solomon and Mathew again [10], proposed that hemicrania continua (HC) should be added to these three forms and that each of the four forms thus identified should be distinguished depending on the presence or absence of medication overuse. They also set precise diagnostic criteria for each form. TM criteria are reported in Table 1.

In 1995, following the description of a broad case series of CDH patients seen at the Parma and Pavia headache centres in Italy, Manzoni et al. [11] first introduced the name "chronic migraine" (CM), which they included, alongside migraine with interparoxysmal headache (MIH), within the migraine forms that evolve unfavourably over time until they lose the typical symptom-free interval between an attack and the next. According to the Italian authors, CM and MIH differentiate from each other for the type of headache that sets in the originally free intervals between attacks: while retaining the clinical features of migraine in CM, in MIH this interval headache loses its similarities to migraine (in some cases it has the same features of tension-type headache, but in other cases it has undefined features and this prevents it from being definitely included in the migraine or the tension-type headache group).

If we browse the scientific CDH literature produced from the mid-1990s to as late as 2006, we can see how predominant Silberstein et al.'s systematization has become. Nevertheless, we are sorry to say that the 2004's edition of the International Classification of Headache Disorders classification (ICHD-2) [12] only partially—and not always appropriately—integrated those considerations in its final changes over the 1988 first edition of the IHS classification [1].

In the first place, the ICHD-2 [12] editors did not deem it advisable to devote a separate chapter to CDH within their classification. CTTH, already included in the 1988 first edition of the IHS classification [1] was recognized again in the 2004 ICHD-2 classification [12]. HC and NDPH were included in the ICHD-2 classification [12], and they were coded to Group 4 "Other primary headaches". TM was not recognized as such in the ICHD-2 [12] which, however, included for the first time CM and its diagnostic criteria, coded to 1.5.1 as a complication of migraine (Table 2). Thus, with respect to the most important and certainly most frequent of all CDH forms, i.e., migraine evolving unfavourably over time, the ICHD-2 [12] eventually retained the CM name, originally proposed by Manzoni et al. [11], but with diagnostic criteria that are very different from those suggested by the Italian authors.

Additionally, the ICHD-2 [12] prefers to retain medication-overuse headache as an autonomous clinical entity (coded to 8.2 of the 2004 classification).

Table 1 Diagnostic criteria for transformed migraine by Silberstein et al. [10]

(A) Daily or almost daily (>15 days/month) head pain for >1 month

(B) Average headache duration of >4 h day (if untreated)

(C) At least 1 of the following:

1. History of episodic migraine meeting any HIS criteria 1.1–1.6
2. History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months
3. Headache at some time meets HIS migraine criteria 1.1–1.6 other than duration

(D) Does not meet criteria for new daily persistent headache or hemicrania continua

(E) At least 1 of the following:

1. There is no suggestion of one of the disorders listed in groups 5–11
2. Such a disorder is suggested, but it is ruled out by appropriate investigations
3. Such a disorder is present, but first migraine attacks do not occur in close temporal relation to the disorder

Table 2 Diagnostic criteria for chronic migraine by the ICHD-2 (2004) and by the ICHD-2R (2006)

ICHD-2 (2004)

(A) Headache fulfilling criteria C and D for migraine without aura on ≥15 days per month for >3 months

(B) Not attributed to another disorder

ICHD-2R (2006)

(A) Headache (tension-type and/or migraine) on ≥15 days per month for ≥3 months

(B) Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 migraine without aura

(C) On ≥8 days per month for ≥3 months headache has fulfilled C.1 and/or C.2 below; that is, has fulfilled criteria for pain and associated symptoms of migraine without aura:

1. Has at least two of a–d:
   (a) Unilateral location
   (b) Pulsating quality
   (c) Moderate or severe pain intensity
   (d) Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

   And at least one of a or b below:
   (a) Nausea and/or vomiting
   (b) Photophobia and phonophobia
2. Treated and relieved by triptan(s) or ergot before the expected development of C.1 above

(D) No medication overuse and not attributed to another causative disorder

Since its inclusion in the ICHD-2 classification [12], then, CM has always appeared as an ambiguous clinical entity and one that would not be of much use either for clinical practice or research.

As defined by the diagnostic criteria of the ICHD-2 classification [12], CM seems: (a) to resemble more a high-frequency migraine than a migraine evolving negatively over time; (b) to be scarcely relevant to actual clinical practice [13].

Another major shortcoming of the ICHD-2 classification [12] is that most CDH patients receive multiple diagnoses, in several cases as many as four or five, including some that are only probable. Since the very introduction of the ICHD-2 [12] in 2004, then, it has been clear that the diagnostic criteria of CM needed to be changed.

Current official classification of CM: merits and critical issues

Even the committee that worked them out was aware of this problem and new criteria were formulated as a result (ICHD-2R) [14]. Today, these criteria (Table 2) are considered standard reference and, according to Olesen [15], all of them could be integrated in the future ICHD-3 classification.

The new criteria [14] are much more relevant to actual clinical practice than the previous ones of the ICHD-2 classification [12]. Nevertheless, two relevant questions remain to be solved: the first one is that a severity gradient exists in CM, as defined in the ICHD-2R classification [14] diagnostic criteria, and it is so wide-ranging as to carry the risk of including exceedingly different cases under the single group of CM. The second major question is the problem of symptomatic medication overuse, which affects most patients with CM [16]. According to the ICHD-2R classification [14], a patient with a form of migraine that has worsened over the years or has become complicated evolving into daily or near-daily, with daily or near-daily use of symptomatic drugs, should have a dual diagnosis: medication-overuse headache and probable CM. Instead of a dual diagnosis, would not a single diagnosis of CM with medication overuse be preferable in such a patient until he/she is freed from the overused drugs?

A new proposal for redefinition of CM

The next edition of the ICHD classification (ICHD-3), due out by the end of 2012, will certainly introduce some changes to CM as defined in the ICHD-2 classification [12] (Table 2).

The term "chronic migraine" seems ambiguous and inaccurate, even if it has become "familiar" to headache researchers. The term "transformed migraine" is to be preferred, because it is more indicative of the type of patients we are referring to [9, 10]. The 3-month period generally taken as reference until now seems too short and carries the inherent risk of considering TM as a form of migraine that merely undergoes an entirely transient worsening. A 1-year period seems more appropriate.

The same applies to the other temporal parameter, which must define and therefore better specify the vague expression "daily or near-daily" originally used by Mathew et al. [2, 3]. Quantifying this daily or near-daily parameter as $\geq$15 days appears an oversimplification. In order to avoid too loose a categorization, a more accurate statement would be $\geq$20 days/month, adding also that there are never >5 headache-free consecutive days.

A basic reason that could explain why, in spite of the efforts made by so many authors for so many years, we have not yet come to share a common systematization for the classification of migraine that evolves unfavourably, is that international classifications are typically classifications

Table 3 Proposed revision of the ICHD-2 for migraine

1.1 Migraine without aura
1.1.1 Infrequent migraine without aura
(A) Headache fulfilling criteria C and D for 1.1 migraine without aura on $\leq$3 days/month for $\geq$3 months
(B) Not attributed to another disorder
1.1.2 Frequent migraine without aura
(A) Headache fulfilling criteria C and D for 1.1 Migraine without aura on >3 but <10 days/month for $\geq$3 months
(B) Not attributed to another disorder
1.1.3 Very frequent migraine without aura (or chronic migraine?)
(A) Headache fulfilling criteria C and D for 1.1 migraine without aura on $\geq$10 but $\leq$20 days/month for $\geq$3 months
(B) Not attributed to another disorder
1.1.3.1 With medication overuse
1.1.3.2 Without medication overuse
1.5 Complications of migraine
1.5.1 Transformed migraine
(A) Headache (tension-type and/or migraine) on >20 days/month for $\geq$1 year and never with more than 5 headache-free consecutive days
(B) Occurring in a patient who has had at least five attacks fulfilling criteria for 1.1 migraine without aura
(C) On $\geq$10 days per month for $\geq$1 year headache has fulfilled criteria for pain and associated symptoms of migraine without aura or patient has been successfully treated with an ergot or triptan
(D) Not attributed to another disorder
1.5.1.1 With medication overuse
1.5.1.2 Without medication overuse

of headache attacks. Hopefully, in the future we will be able and willing to engage in the preparation of a classification of headache syndromes that may combine all current international headache classifications. Waiting for this goal to be achieved, we think it reasonable to formulate a simple and practical proposal, which can be broken down as follows:

(a) Differentiation of migraine without aura based on frequency of attacks, with the addition of a third-digit level (Table 3).
(b) Introduction of precise temporal parameters among the diagnostic criteria for the three migraine without aura subtypes (infrequent, frequent and very frequent) (Table 3).
(c) Inclusion of TM among the complications of migraine: TM should be coded to 1.5.1 replacing CM and its diagnostic criteria should be different from those listed in the ICHD-2R [14] (Table 3).
(d) Differentiation of TM at the fourth-digit level depending on the presence or absence of symptomatic medication overuse (Table 3) regardless of whether overuse played any role in the worsening of the headache.
(e) Shifting of medication overuse headache to the Appendix with alternative diagnostic criteria to be defined.

It would be discuss if introduce the concept of "refractory" or "unresponsive" CDH.

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

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Sinus venous stenosis, intracranial hypertension and progression of primary headaches

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Abstract The recently advanced hypothesis that idiopathic intracranial hypertension without papilledema (IIHWOP) is a powerful risk factor for the progression of pain in individuals prone to episodic primary headache implies that IIHWOP is much more prevalent than it is believed to be in the general population and that it can run almost asymptomatic in most of the affected individuals. In this review, we discuss the evidence available supporting that: (a) sinus venous stenosis-associated IIHWOP is much more prevalent than believed in the general population and can run without symptoms or signs of raised intracranial pressure in most of individuals affected, (b) sinus venous stenosis is a very sensitive and specific predictor of intermittent or continuous idiopathic intracranial hypertension with or without papilledema, even in asymptomatic individuals, (c) in primary headache prone individuals, a comorbidity with a hidden stenosis-associated IIHWOP represents a very common, although largely underestimated, *modifiable* risk factor for the progression and refractoriness of headache.

Keywords Chronic migraine · Chronic daily headache · Idiopathic intracranial hypertension · Idiopathic intracranial hypertension without papilledema · Self-limiting venous collapse · Sinus venous stenosis · Review

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Progression of headache as a spontaneously reversible event

The prevalence of chronic daily headache (CDH) in the population ranges between 4 and 5 %, the migraineous subtype alone accounting for 1.3–2.4 % [1–3]. Therefore, these conditions are recognized as a dramatic worldwide health problem, with a deep disabling impact and high direct and indirect social costs [4–6]. According to the International Headache Society's definition, chronic tension type headache (CTTH) evolves from a previously episodic form [7]. Various evidences indicate that episodic migraine may also progress towards a chronic form in some patients [8–11]. The progression of migraine is characterized by the increase in headache frequency and duration, often parallel to reduced pain intensity and accompanying symptoms. Usually, the process extends over months or years, ultimately leading to continuous mild pain with superimposed exacerbations of moderate to severe migraineous pain. In some patients, the shift may be much faster or even abrupt. In such cases, the clinical presentation might be undistinguishable from the recently proposed "migraineous" variant of New Daily Persistent Headache (NDPH) [12]. If headache escalates to a chronic course, recent studies indicate that chronic headache may spontaneously remit in some patients, returning to the previous episodic pattern of attacks. A longitudinal survey [10] has shown that infrequent primary episodic headache sufferers (2–104 days per year) carry a 6 % annual risk of progressing to a frequent episodic pattern (105–179 days per year) and a 3 % annual risk of developing a chronic condition (180 or more days per year). Interestingly, in the same study, a return to a frequent or infrequent episodic pattern (less than 180 days per year) was observed in 57 % and to less than 1 attack per week in 14 % of the chronic

sufferers. The relatively high frequency of spontaneous return to an episodic pattern of headache highlighted by this paper is confirmed by the findings of a recent 3-year prospective population study [13]. A population sample of 383 individuals diagnosed with chronic migraine (CM) in 2005 underwent diagnosis revision in 2006 and 2007. Only 33.9 % of the patients had a stable course of CM throughout the 3 years. In 26.1 % of the sample, a remission of CM (i.e. the return to an episodic pattern) was observed in both the subsequent years, while an intermediate "transitional" condition was recorded in the remaining 40.0 % of the samples. Remission predictors included a lower number of headache days/month at the baseline and notably, the absence of allodynia. Unexpectedly, the preventative treatment not only did not predict the remissions, but it was associated with a lower probability of remission. The more intense and disabling the condition, the more likely it is to receive a preventative treatment; this finding could reflect a selection bias. Still, these data challenge the clinician's belief in the actual efficacy of CM treatments [14].

According to the above findings the progression of headache should be considered a dynamic and, above all, a *spontaneously reversible* event. These observations highlight the need for a prompt identification of the population at risk and of the factors associated with both the progression of headaches and the return to an episodic pattern.

Cerebral sinus venous stenosis and idiopathic intracranial hypertension

Stenosis of large cerebral venous sinus is strongly suspected to play a causative role in idiopathic intracranial hypertension with (IIH) or without papilledema (IIHWOP) and have been extensively investigated in the recent years. Although the debate is not yet concluded, evidence available clearly indicates that significant sinus venous stenosis can be observed in as many as a quarter of otherwise healthy individuals in the general population [15, 16]. Moreover, sinus venous stenosis in magnetic resonance venography (MRV) is a reliable predictor of continuous or intermittent intracranial hypertension, with 93 % sensitivity and specificity [17]. This means that the finding of significant stenosis predicts with high probability the presence of CSF (cerebrospinal fluid) hypertension even in asymptomatic individuals [18, 19].

Based on these observations, we have recently proposed [20] that a clinical and epidemiologic "continuum" might exist between: (a) IIH with papilledema, a condition observed infrequently, probably representing only the tip of the iceberg [21]; (b) symptomatic IIHWOP, presumably largely misdiagnosed and/or underdiagnosed at present; and (c) asymptomatic IIHWOP (a-IIHWOP), a completely hidden condition with an extraordinarily high prevalence among "healthy" individuals, actually comparable with the reported population prevalence of sinus venous stenosis, about 20–25 % [15, 16].

The "self-limiting venous collapse" feedback loop mechanism in IIH pathogenesis

The putative mechanism leading to the increase of intracranial pressure (ICP) in sinus stenosis carriers has been described in detail elsewhere [22]. Briefly, it relies on a "self-limiting venous collapse" (SVC) positive feedback-loop engaged between CSF and venous blood pressure in presence of abnormally collapsible sinuses walls [22, 23]. Since CSF pressure is normally higher than cerebral venous pressure, even in physiologic conditions a collapsible vein will unavoidably collapse, impeding blood outflow and leading to an increase in venous pressure above the compression level. The subsequent decrease of the physiologic CSF/blood pressure gradient reduces the CSF outflow rate, consequently increasing the CSF pressure. In the presence of collapsible central veins, this contributes to further venous narrowing and generates a positive feedback loop that leads to the coupled increase of venous and CSF pressures [24], a phenomenon not expected in the presence of sufficiently rigid sinus walls [23]. The positive feedback loop stabilizes when the maximum collapsibility degree of sinus walls has been reached. Therefore, provided an abnormal collapsibility of sinuses is present, the SVC mechanism allows the generation of a new relatively stable state of balance between the central venous pressure and the CSF pressure, but at higher values [22]. The new higher pressure balance is self-limiting, self-sustaining, and above all, it is *reversible* under specific circumstances. In fact, the higher pressure balance state may shift towards the normal pressure status provided an adequate perturbation is carried to whichever side of the loop. This gives reason, on one hand, for the high reported efficacy of stenting the collapsed veins [25–30] and, on the other, for the frequently observed long-term remissions of IIH after even a single lumbar puncture with CSF subtraction [31–33].

IIHWOP and headache progression

The clinical presentation of IIHWOP may be limited to a mild to moderate continuous headache, thus resembling a CTTH [34]. However, in most cases, superimposed recurrences of severe migraineous pain are reported, leading to a picture indistinguishable from that of transformed migraine (TM) [35]. According to the results of the first systematic study on the coexistence of IIHWOP in chronic headache

sufferers [36], obesity and pulsatile tinnitus predicted CSF hypertension while the headache profiles of CDH patients with IIHWOP did not differ from that of chronic headache sufferers without evidence of raised CSF pressure. As a consequence, IIHWOP is frequently misdiagnosed as TM/CM [35–37]. There is evidence that, in migraine patients, sinus venous stenosis predicts the presence of IIHWOP [38]. IIH may occur without headache in non-migrainous individuals or in the course of a well known migraine protective factor such as pregnancy [39], suggesting that a CM-like clinical presentation of IIHWOP could require a migraineous predisposition. IIH and CM share some relevant risk factors such as: female gender, obesity and sleep disturbances [40–42]. Moreover, topiramate, a drug with growing evidence of efficacy in CM [43, 44], shares with acetazolamide the inhibiting property of carbonic anhydrase isoenzyme [45]. Acetazolamide reduces intracranial hypertension and is widely used in IIH treatment [46]. In addition, topiramate has been found effective in IIH treatment [47, 48] resulting as effective as acetazolamide in a recent comparative study [49]. This has raised the hypothesis that the efficacy shown by this drug in CM treatment could be related, at least partially, to an acetazolamide-like CSF pressure lowering effect. This hypothesis is supported by a recent report [50] showing that a single 200 mg oral dose of topiramate is immediately followed by a significant drop in CSF pressure in headache patients.

The reported considerations and data indicate that IIHWOP and chronic headaches are often comorbid, share overlapping clinical presentations and risk factor profiles, and are both responsive to topiramate. Taken together, these analogies raise the question of a pathogenetic link between the two conditions and support the hypothesis that a hidden sinus stenosis-associated IIHWOP comorbidity could represent a powerful risk factor for headache progression in migraine patients.

This hypothesis implies: that sinus venous stenosis are much more prevalent in chronic headache patients than expected, that they can sustain a hidden IIHWOP in most of the cases, and that treatment of the intracranial hypertensive status might be followed by a longstanding return to an episodic patterns of attacks. A recent study on 98 consecutive cases of unresponsive chronic headache evaluated with MRV before 1 h ICP-monitoring strongly supports the above hypothesis [18]. The series included cases of CM and CTTH in comparable proportions together with a minority of ''other forms''. Bilateral-transverse sinus stenosis was found in 48.9 % of the chronic-headache sufferers' sample. A continuous or intermittent IIHWOP was detectable in most of the stenosis carriers (91.6 %) and in none of the chronic-headache sufferers with normal MRV. Moreover, after the lumbar puncture, a transient (2–4 weeks) improvement in headache frequency has been observed in majority of the intracranial hypertensive subjects. These findings strongly suggest that subjects prone to primary headache, carrying central venous outflow abnormalities are at a high risk of developing continuous or intermittent comorbid IIHWOP. Possibly due to a central sensitization sustained by inappropriate subcontinuous firing of the nociceptive network at congested vein level [21], this comorbidity leads to the onset of a subcontinuous interval pain and increased frequency of painful attacks, up to a presentation indistinguishable from migraineous or tension-type chronic daily-headache or medication-overuse headache.

The possible periodical activation/deactivation of the SVC mechanism might explain the recently reported high frequency of spontaneous CM remissions. It can also shed some light on the growing clinical and taxonomic challenge represented by "migraneous NDPH" [12].

Comments

Based on the available data, several hypotheses with a potentially high clinical impact can be formulated.

1. In most of the central sinus stenosis carriers the proposed SVC mechanism sustains a mild, and usually asymptomatic IIHWOP. The prevalence of asymptomatic IIHWOP in the general population is therefore much higher than it is believed to be. Accordingly, cases with papilledema might represent only the small *visible* part of a *hidden and* much larger phenomenon.
2. In primary episodic headache subjects, comorbid IIHWOP represents a powerful and very common, albeit largely underestimated, *modifiable* risk factor for the progression and refractoriness of pain. Probably due to the continuous nociceptive firing arising from the congested veins, a comorbid IIHWOP could represent the pathogenetic key leading to a central sensitization–related progression of pain. According to the available data, this mechanism could refer to up to one half of the primary chronic headache sufferers with minimal response to treatments that refer to specialized headache clinics.

Due to the potential clinical and taxonomic impact of these assumptions, their field testing in adequately designed environment is urgently needed.

Conflict of interest None.

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Medication overuse headache (MOH): complication of migraine or secondary headache?

L. Grazzi · G. Bussone

Abstract In the field of chronic forms of headache, medication overuse headache (MOH) seems to be a problematic argument as the correct position of this clinical condition in the International Headache Society (IHS) classification is not clear yet. In 1988, when IHS organized the first classification of the different forms of headache, the clinical problem of medication overuse was included in the section eight of the IHS; during the last decades the criteria of the classification changed, and now this form is included in the classification system as a clinical condition distinguished from chronic migraine and other chronic forms of headache. The different models of classification are discussed and the clinical and practical aspects are considered in this paper.

Keywords Medication overuse headache · Chronic migraine · IHS classification

Introduction

The definition of medication overuse headache (MOH) remains a problematic question: we know that this is a form of headache, with high frequency of attacks, complicated by excessive use of analgesics.

The IHS classification proposed in 1988 the term of drug-induced headache for forms of headache related to overuse of different kinds of substances (section eight of the classification of IHS 1988) [1] and it was conceived as the evolution of headache induced by the overuse of difference substances as symptomatic medications.

Many criticisms have been attributed to this classification as it has been considered not adequate to the clinical condition: when a problem of medication overuse is evident, it is necessary to emphasize the regular intake of drugs as the basis of drug-induced headache, also considering that this clinical condition includes different and heterogeneous forms of headache pain.

Before the IHS classification in 2004 [2], while clinicians and researchers were looking for the best definition of chronic forms of headache, in presence or not of overuse of medications, Silberstein and Lipton [3] proposed to classify chronic forms by using a classification system where different kinds of headaches (tension type headache or migraine) evolved from episodic to chronic (transformed migraine was defined a form of migraine without aura evolved from episodic to chronic) and all of them were distinguished with or without medication overuse. Nevertheless, after few years, in 2004 [2], IHS included chronic migraine in the classification (CM) as a complication of a migraine form and introduced the new term of MOH: in this specific case, the definition was made according to different clinical symptoms caused by the intake of different categories of drugs.

Consequently, the term MOH was applied in clinical practice as there were evidences that most of the drugs used for treating headache may induce a MOH in patients suffering from primary headache disorders.

The categories of drugs involved in MOH are different and they change according to cultural differences and other factors.

In the most part of cases, the responsibility of developing MOH is not due to a single pharmacologic medication, as patients suffering from chronic forms of migraine use different medications or their combinations to treat

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their attacks. All the symptomatic compounds used for migraine may favour the onset of MOH, and also symptomatic drugs such as triptans have been considered to induce MOH. Probably the group of patients with MOH induced by triptans is going to increase in the next future, particularly in younger migraine sufferers as the consumption of triptans is increasing significantly.

As MOH is considered by the IHS a particular clinical condition, a form of high-frequency of migraine where the principal component inducing headache attacks is represented by the overuse of medications, the diagnosis of this form of headache no longer requires that headache resolve or revert to its previous patterns within 2 months after discontinuation of the overused medication. On the basis of this characteristic, the diagnosis of MOH is possible after withdrawal of the offending medications.

It is difficult to see patients suffering from chronic migraine (CM) who do not use medications for their attacks and for treating pain: when pain is present, at least 15 days per month, patients will likely report medication overuse as a consequence, if not necessarily a cause inducing chronicity.

The withdrawal program, also if there is no universal consensus on it, is able to return these patients to a regular headache temporal pattern, but often patients need to be followed periodically, with preventive treatment and other different non-pharmacological approaches to obtain a significant clinical improvement and an effective therapeutic approach.

On the basis of the new revision of IHS 2006 [4], the dual diagnosis of "Medication Overuse Headache" on one hand and of "Probable Chronic Migraine" on the other, seems to be not so effective from the clinical point of view and the discussion about it remains open: the question could be resolved simply with a single diagnosis of chronic migraine with medication overuse, as Manzoni [5] suggested in a recent paper.

MOH can be a complication of migraine without aura, when this kind of migraine evolves from an episodic to a chronic form aggravated by the overuse of analgesics. Nevertheless, some uncertainties remain about MOH, related to the lack of specific scientific data on the role that the individual symptomatic drug used by patients might play on the underlying course of the disease, if overused.

Patients suffering from CM, as defined in the last revision of the IHS in 2006 [4], report headache often associated with medication overuse and the indicator of treatment success should be the 50% reduction in frequency of days with headache per month as in episodic migraine without aura.

This would be a useful measure to evaluate the efficacy of preventive treatment for chronic migraine.

If comorbidities are present, and this is not unusual in chronic forms with or without medication overuse, they also need to be recognized and adequately treated after considering that drugs used in treating headache in the presence of comorbidities are often not the first choice or that the dosages have to be modified in a specific way.

Conclusion

From these considerations we can deduce that in the near future it will be necessary to achieve a consensus for the definition of the different forms of chronic headaches. Thus, we can clearly identify MOH and effective treatments for it that prevent it from becoming intractable.

Clinicians are often involved in taking care of problematic patients suffering from migraine at high frequency, complicated by medication overuse, by assisting them and managing their different problems so the necessity to classify correctly the different forms is important, but may be secondary with respect to the clinical problem.

The question of whether we can consider MOH a distinguished form of secondary headache or simply a complicated form of migraine with character of chronicity, remains a problem to clarify and to discuss within the IHS committee, but it is necessary that our primary goal as clinicians is to take care patients. There are different pathogenetic factors involved in chronicity and in medication overuse and these factors can influence therapeutic approaches. So it will be necessary to pay attention to the evolution of IHS classification system for better identification of all these forms, but also it will be likely that the IHS committee consider carefully the clinical aspects involved by treating these problematic clinical conditions.

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

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Peripheral neuromodulation in chronic migraine

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Abstract Patients with chronic migraines are often refractory to medical treatment. Therefore, they might need other strategies to modulate their pain, according to their level of disability. Neuromodulation can be achieved with several tools: meditation, biofeedback, physical therapy, drugs and electric neurostimulation (ENS). ENS can be applied to the central nervous system (brain and spinal cord), either invasively (cortical or deep brain) or non-invasively [cranial electrotherapy stimulation, transcranial direct current stimulation and transcranial magnetic stimulation]. Among chronic primary headaches, cluster headaches are most often treated either through deep brain stimulation or occipital nerve stimulation because there is a high level of disability related to this condition. ENS, employed through several modalities such as transcutaneous electrical nerve stimulation, interferential currents and pulsed radiofrequency, has been applied to the peripheral nervous system at several sites. We briefly review the indications for the use of peripheral ENS at the site of the occipital nerves for the treatment of chronic migraine.

Keywords Chronic · Migraine · Peripheral · Nerve · Stimulation

Introduction

Patients with chronic daily headaches and chronic migraines (CM) report remarkable impacts on everyday functioning and show high disability scores [1]. CM is a disabling condition prevalent in around the 2 % of population [2] and it includes transformed migraines that are considered as a migraine complication [3]. Several papers have addressed the definition of intractable headaches using specific criteria for severity of disability and pharmacological treatment failures [4–6]. However, there are no prospective trials validating the definition of refractory migraine (RM). The proportion of patients with RM attending headache treatment units is 5.1 % with a mean MIDAS score of 96; almost 40 % of these patients experience medication overuse [7]. Therefore, a huge population of patients could theoretically be candidates for an invasive procedure to reduce the pain associated with this disabling condition. More recently, Silberstein et al. proposed four classes (mild, moderate, severe and very severe) of intractability based on patients' responses to preventive treatments. Class 3, severe, is the failure to adequately respond to treatment trials of three different drugs [e.g. b-blockers, tricyclic antidepressants, calcium antagonist (verapamil or flunarizine), sodium valproate, topiramate and combination therapy]. The definition of class 4, very severe, includes the class 3 and the failure to respond to aggressive infusion or inpatient treatment and/or the failure to respond to detoxification treatment in subjects with medication overuse [8]. Electric nerve stimulation (ENS) is a familiar concept in the pain research field appearing in the Medline for the first time in 1948 [9]. For a detailed review exploring the pathophysiology of intrinsic head pain, the functional relationship of central and peripheral structures and theoretical mechanisms of neurostimulation, we suggest the review of Jenkins et al. [10]. We center our attention on the peripheral stimulation technique at the site of the occipital nerves for the treatment of CM.

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Table 1

Authors diagnosis	Disability measure	O.N.B. positive	Refractory	MOH	*N*	Efficacy	Adverse events	Device	Follow up
Popeney [12] Episodic and transformed migraine	Yes	–	"Refractory to conventional treatment for at least 6 months"	76 %	25	88 % had ≥50 % decreased frequency or severity	36 % had lead migration 12 % had infection	Medtronic synergy	18.3 m
Schwedt [13] CM	Yes	–	"Failure of several preventive drugs either alone or combined"	No	8	50 % had ≥50 % decreased severity	100 % had lead migration at 3 years	Medtronic synergy	19 m
Trentman [14] CM	No	–	Not reported	Not reported	3	2/3 excellent	None	Bion® micro-stimulator	6 m
Saper [10] CM	Yes	Yes	"Failure to preventative medications from at least two different classes of drugs"	No	29	39 % had >50 % decreased frequency >50 % or a decreased severity over 3 points	24 % had lead migration/14 % had infection	Medtronic synergy	3 m
Silberstein [15] CM Probable CM	Yes	No	"Failure to preventative medications from at least two different classes of drugs"	Not reported	105	53 % good or excellent open 65 % good or excellent	19 % had lead migration or malfunction or breakage 12 % infection erosion site complication	St. Jude device	3 m Open 13 m

Methods

We performed a Medline search using the following keywords: chronic, migraine, peripheral, nerve and stimulation.

Results

The search engine retrieved 47 papers. According to our aim, we selected one randomized trial [11]. Furthermore, we performed a search inquiry using the word 'headache' instead of 'migraine' and we selected the other three non-randomized trials [12–14]. Data regarding a second randomized controlled trial presented at Berlin HIS congress in 2011 were added [15]. Results are summarized in the Table 1.

Conclusion

Globally 170 CM patients were treated with occipital nerve stimulation (ONS) in CM. Despite the methodological differences, it seems to be a promising therapy. However, the use of ONS requires careful and accurate selection of patients due to the high cost of the device and the frequent occurrence of lead migration, which can lead to additional surgeries. The proposed definition of severe intractability (Class III) paired with moderate disability scores [8] could be too broad a definition to qualify patients for ONS invasive treatment. Only patients with high disability score and failure to all different classes of preventive treatment [16] should be candidates for invasive procedure. There is a need for future studies using ONS on Class 4 CM patients who experience severe disabilities and are unresponsive to preventive treatments.

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

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Drug-resistant chronic migraine: the Italian GON project

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Abstract Chronic daily headache is a major problem due to severe disability and high socio-economic costs. In the last years, some trials have shown potential benefit from new therapeutic approach by occipital neurostimulation techniques, already applied with some success for the treatment of chronic cluster headache. Due to the extremely heterogeneous population suffering from refractory chronic daily headaches, we propose a national multicenter experimental study involving Italian ANIRCEF Headache Centres with the aim to evaluate the efficacy of occipital neurostimulation in a selected group representative for the drug-resistant chronic migraine. Patients with chronic migraine according to Manzoni's modified IHS criteria-2011, with or without medication overuse headache, will be selected. Duration of illness should be at least 2 years and pharmacological refractoriness defined strictly for experimental-surgical purposes as those patients who have properly tried without success almost all available classes of prophylactic medications. Those presenting with medication overuse should have tried at least two previous detoxification treatments. A full psychopathological assessment will be performed by a psychiatrist, to exclude mainly psychotic disorder, ongoing severe status of an affective disorder, severe post traumatic stress disorder. Headache characteristics and abortive treatments used will be reported daily on a predisposed diary during 3-month baseline and continuously through the post implant follow up, while disability and QoL scale (MIDAS, SF-12) will be completed baseline, 6 and 12 months after implant.

Keywords Neuromodulation · Occipital nerve stimulation · Chronic daily headache · Chronic migraine · Drug-resistant headache

Introduction

In spite of the advances in the knowledge of pathophysiology and management of headache, it remains evident that a large proportion of patients develop a chronic form that sometimes results refractory to any medical treatment.

The chronic daily headache prevalence is 3–5 % in the general population and refractoriness is estimated to be encountered in 10 % of them.

There is a clear need for novel approaches for the management of these highly disabled patients.

Background

In line with the experience derived from the application of neurostimulation techniques in TACs, and especially, refractory chronic cluster headache that have shown worldwide sustained favourable effect in a consistent proportion of otherwise pharmacologically intractable patients with both central hypothalamic and peripheral occipital neurostimulation approaches [1, 2], these techniques have been tried also in other chronic pain condition including chronic daily headache [3].

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Peripheral and central neuromodulation approaches resulted well-tolerated but undoubtedly much safer in the former.

Several case series, usually retrospective reports, with ONS have been performed in chronic headache including both a variety of primary headache and secondary such as cervicogenic headache, occipital neuralgia and post traumatic headache [4–6].

This background and these pioneer observations prompted research trials to investigate safety and efficacy of neurostimulation device: at present three large randomized sham controlled clinical trials are still going on [7–9] and final efficacy data are yet to be published.

Preliminary data have been presented arising many criticisms by those already experienced in this field, mainly because of patient selection bias in otherwise well-designed studies.

In fact, chronic daily headache nosology is a challenge and a matter of debate since long time, still controversial as the ICHD-2R 2006 did not deal with it definitely, leaving room for overlapping entities.

At the very beginning of the application of ONS, patient have been selected on the basis of pain location with a component on the back of the head [4, 7, 9], sometimes conditioned by prior evidence of response either to peripheral anaesthetic block [5] or to a short-term trial of occipital PNS with an externalized system [6].

Both these strategies showed to be unuseful and without any influence on the outcome, while they may have introduced a bias in patient selection as pain on the back of the head is not representative for most migraine patients and as the efficacy has been evaluated on such a short-term period.

Furthermore, the perception of paresthesia from the initial activation of occipital nerve stimulation, useful to guide surgeon to the appropriate placement of electrodes and considered of relevance for the outcome, quite early will fade away as habituation will take place.

This could be important for different strategies of neurostimulation, cycling rather than continuous, to preserve from habituation effect, but it is not known if even subthreshold stimulation might be effective for pain relief.

No unique setting of stimulation has been proved to be more effective: both low or high frequency stimulation, short or long pulse width, low or high amplitude, showing that efficacy is not ground on presumed established neurophysiological mechanisms.

Actually the main impression is that we do not know exactly which kind of headache patient has been implanted, because, the definition of chronic daily headache obviously does not clarify at all the nature of the disorder, encompassing an extremely heterogeneous variety of different clinical entities.

The lack of clear diagnostic definition of patient selected, the outcome sometime suspiciously declared enthusiastic with rapid improvement within days to weeks compromise the evidence of any efficacy of the occipital nerve stimulation treatment.

We are aware of the experience in our Centre with occipital nerve stimulation in very few subjects—four female patients—implanted under the compulsion of compassionate base in totally disabled patients with chronic daily headache since many years, overwhelmed by a huge consumption of painkillers and an absolutely poor quality of life complicated by a depressive state and a condition of complete isolation in the daily living. After more than 4 years, the outcome has been very disappointing with a failure of reaching any substantial improvement, exception for one of them with only a relative success. For one patient, has been necessary to remove the device because of skin erosion at the occipital site.

The evidence is that a very long history of the illness duration, a complex psychopathological comorbidity especially in term of previous life events or enduring stressors, moreover, if concomitant with personal condition of solitude in the total absence of any familial or partner support, all were negative prognostic factors heavily conditioning any potential improvement, furthermore, confirming the migraine nature as a bio-psychosocial disorder.

After that, we agreed on the importance to select more treatable patients, with the need to exclude actually the most difficult ones, although paradoxically also the most needy.

Only in the case we will be able to show the efficacy of occipital nerve stimulation in a more selected and homogeneous group of migraine patients, than we could better evaluate how to improve the efficacy in more difficult ones.

When chronic migraine should be considered drug resistant?

Another main limitation encountered in the previous reports on occipital nerve stimulation in chronic headache has been the definition of refractoriness to medical treatments.

The criteria for medical refractoriness are far from being univocally recognised. The definition may assume quite different meaning according to the purpose we want to apply: it's quite different if the question is, i.e., referral to a tertiary level Headache Centre specialist or to select patients to even minimally invasive surgical techniques of neurostimulation.

Because of the high vulnerability of disabled chronic daily headache patients, this point is of outstanding importance for ethical reasons [10]. We have already

Table 1 Proposed diagnostic criteria for chronic migraine by Manzoni et al. [11]

1.1.3 Chronic migraine
A. Headache fulfilling criteria C. and D. for 1.1 Migraine without aura on $\geq$10 but $\leq$20 days/month for >3 months
B. Not attributed to another disorder
C. Headache has at least two of the following characteristics:
Unilateral location
Pulsating quality
Moderate or severe pain intensity
Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
Nausea and/or vomiting
Photophobia and phonophobia

witnessed and given the warning for a rapid spread of peripheral neurostimulation in chronic headache, in the lack of extensive data proving these techniques to be more effective than the traditional approach.

To overcome the problem of an heterogynous sample and clarify the potential benefit from neurostimulation therapies, we planned a national multicenter study involving Italian Headache Centres for a strict selection of chronic migraine patients according to the criteria based on Manzoni's modified IHS criteria-2011 [11], with or without medication overuse headache, resulting refractory to medical treatment, and thus, potential candidate to surgery.

In line with the ethical criteria for research purpose, we will consider candidate to occipital nerve stimulation those with chronic migraine (Table 1) suffering from headache at least 10 days per month and with illness duration lasting from at least 2 years, a time period long enough for testing several, if not all pharmacological trials of prophylaxis.

We exclude those medication overuse headache patients abusing from ergot, barbiturate or opioid containing analgesics, in whom detoxification treatment and drug-dependence resolution is mandatory, for others, we require the failure of at least two attempt of detoxification treatment before surgery.

We choose not to include a control arm in the study because of the severe including criteria reserved to the disabled patients with a long run-in period and the long-term follow up in relation to the ethical issues in performing sham surgical procedures which expose the patient to surgical risk and discomfort even without any potential benefit.

Aware of the fact that successful outcome remains a matter of combination of proper patient selection and education of the patient in dealing with daily headaches and medication use, we should select treatable patients, with proven compliance and available support from parental members, we then recommend preferably to select already known patients afferent to the Headache Centre and not simply referred from the medical practitioner or specialist not experienced in headache field.

We clearly inform the patients that the neurostimulation most probably will not improve pain as if by magic as soon as it is turned on, but we believe, it could be useful as adjunct in a more complex treatment strategy which goes behind medication treatment only.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

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MIGRAINE AS A RISK FACTOR

Migraine: risk factor and comorbidity

G. Giannini · S. Cevoli · L. Sambati · P. Cortelli

Abstract The burden of migraine strongly increases considering its linkage with other psychiatric, neurological, cardiovascular and cerebrovascular diseases. Migraine is positively associated with many disorders: some are confirmed by several studies whereas others remain uncertain or controversial. The association with some disorders is not simply due to concomitance but it implies a linkage in terms of causality. Highlighting these relationships is important to improve treatment strategies, broaden our knowledge of the pathophysiology and understand if migraine is per se a modifiable risk factor for some disorders.

Keywords Migraine · Comorbidity · Risk factor

Introduction

The burden of migraine includes direct costs, such as medical consultations, emergency visits, hospital admissions and drug intake, but also indirect costs such as missed workdays and impaired work performance. The total burden strongly increases if we consider that migraine is frequently associated with other diseases and that it is an independent risk factor for other complications.

The term "comorbidity" is defined as the statistical association of two distinct diseases in the same individual at a frequency greater than the one expected by chance, while "risk factor" is defined as the element, characteristic, condition or behavior that has been associated with the increased rate of a subsequently occurring disease [1–3].

Migraine is positively associated with many diseases that can increase the perceived severity of symptoms and pose additional challenges for effective patient management. Highlighting this linkage is important to improve treatment strategies, reduce the impaired quality of life and broaden our knowledge of the pathophysiology. There are recognized comorbidities of migraine and others that are still controversial or uncertain. Moreover, some studies have shown that migraine is not only associated with some disorders but it also represents an independent risk factor (Tables 1, 2).

Psychiatric disorders

Relationships between migraine and depression or anxiety have been proved by several studies while associations of migraine with eating, bipolar and other disorders still remain possible [2, 4–8]. The association between migraine and depression is reported to be bidirectional [2, 9]. A recent meta-analysis showed an overall odds ratio of depression in patients with migraine of 2.2 (95 % CI 2.0–2.3) compared to people without migraine. The prevalence of depression ranged from 8.6 to 47.9 % in migraineurs versus 3.4–24.4 % in non-migraine controls [2, 4]. Moreover, migraine with aura (MA) seems to be significantly associated both with depression and suicide attempt [5].

The association between anxiety and migraine was noted in both clinic and community-based studies [2, 10, 11]. Some studies have focused on anxiety subtypes showing that migraineurs have a fivefold greater risk for

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Table 1 Comorbidities of migraine

Disorders	M (%) vs. HC (%)	M vs. HC. OR	MA (%) vs. MO (%)	Migraine in condition sufferers	Notes
Psychiatric					
Depression	8.6–47.9 vs. 3.4–24.4	1.8–4.4	32.2–45.5 vs. 21.7–31.9	–	A
Anxiety	9.1–24.6 vs. 2.5–12	1.61–3.13	57.6 vs. 50.7	OR = 6.88	A
Panic	9.5–17.4 vs. 4.2–5.5	1.94–2.37	–	–	A
Bipolar disorders	8.6–8.8 vs. NA	–	–	13–77 %	B
Eating disorders	39 % vs. NA	–	–	28–74.3 %	C
Neurological					
Restless legs syndrome	11.4–17.3 vs. 1.8–5.6	3.5	–	–	A
Narcolepsy	–	–	–	21.9–37 %	C
Epilepsy	1.0 vs. 0.5	1.41	0.9 vs. 0.6	PR = 1.36; OR = 1.39	B
Cardiovascular					
Patent foramen ovale	39.8–72.0 vs. 25	1.87–5.88	40.9–72.0 vs. 16.2–33.7	22.3–64.3 % OR = 1.82–5.88	A
Atrial septal defects	–	–	–	29.3–30 %	B
Pulmonary AVMs	–	–	–	38–45.2 %	B
Mitral valve prolapse	25 vs. 2.4	–	25–31 vs. 25	27.80 %	B
Atrial septal aneurysm	13.3 vs. 3.2	–	28.5 vs. 3.6	–	B
Congenital heart disease	–	–	–	45.3	B
Hypertension	14–33.1 vs. 16–27.5	0.59–1.4	13–19 vs. 15–17	–	C
High total cholesterol	16.0–32.7 vs. 14.0–25.6	1.09–1.4	18–52.2 vs. 14–37.8	–	B
Obesity >30 kg/m^2	16.9 vs. 19.6	–	–	11.8–28.4 %	C
Cerebellar structural lesions	5.4 vs. 0.7	7.1	–	–	B
Other					
Fibromyalgia	16.8–35.6 vs. 2–8	–	–	45–48 %	A
Chronic fatigue syndrome	66.7 vs. NA	–	–	39–84 %	B
Asthma	16.8 vs. 13.1	1.26	–	15.3–15.5 %	B
LES	–	–	–	21–66.1 %	C

The values represent ranges, from highest to lowest, found in the literature (PubMed)

M migraineurs, *HC* healthy controls, *MA* migraineurs with aura, *MO* migraineurs without aura, *NA* not available, *OR* odd ratio, *PR* prevalence ratio, *A* confirmed by several studies in large sample, *B* uncertain: few studies in small sample, *C* contradictory results

Table 2 Migraine as a risk factor for other diseases

Disorders	M vs. HC	MA vs. MO. RR	Notes
Ischemic stroke	RR = 1.73 (1.31–2.29) –2.16 (1.89–2.48)	2.16–2.27 (1.53–3.19) vs. 1.23–1.83 (0.86–3.15)	A
Transient ischemic stroke	RR = 2.34 (1.90–2.88)	–	B
Hemorrhagic stroke	RR = 1.18 (0.87–1.60)	–	B
Angina	RR = 1.29 (1.12–1.47)	1.71 (1.16–2.53) vs. 1.12 (0.75–1.66)	C
Myocardial infarction	RR = 1.12 (0.95–1.32)	2.08 (1.30–3.31) vs. 1.22 (0.73–2.05)	C
Death from CVD	RR = 1.03 (0.79–1.34)	2.33 (1.21–4.51) vs. 1.06 (0.46–2.45)	B
Cerebellar structural lesions	–	1.9 (1.4–2.6) vs. NA	B
Depression	OR = 2.4–5.8; HR = 1.8–4.2	–	B
Panic	HR = 3.55	–	B
Asthma	OR = 1.17	–	B

The values represent ranges, from highest to lowest, found in the literature (PubMed)

M migraineurs, *HC* healthy controls, *MA* migraineurs with aura, *MO* migraineurs without aura, *NA* not available, *CVD* cardiovascular disorders, *RR* relative risk, *HR* hazard ratio, *OR* odd ratio, *A* confirmed by several studies in large samples, *B* uncertain: few studies in small samples, *C* contradictory results

obsessive-compulsive disorders and noting that there is a bidirectional association between migraine and panic disorders [2, 4, 5]. It has been proved that chronic daily headache is associated with higher rates of depressive and anxiety disorders compared to episodic headache: the more frequent the migraine, the stronger the relationship between the two [4, 5].

Neurological disorders

Migraine and sleep problems

Many studies have investigated the relationship between headaches in general and sleep problems, some focusing on migraine and showing a strong linkage with restless legs syndrome [2, 3, 12, 13], excluding MA [14]. The association between narcolepsy and migraine remains controversial [2]. Some studies have investigated the association between headache and other sleep disturbances such as daytime sleepiness, insomnia, snoring and/or apnea, but few have focused on migraine. One study showed that chronic migraineurs had a high prevalence of sleep complaints and that these can be an independent risk for headache chronification [15].

Migraine and epilepsy

The relationship between migraine and epilepsy remains uncertain. The higher prevalence of migraine in epilepsy patients identified by some studies was not subsequently confirmed [2, 16, 17]. Even if the association remains controversial, there are many similarities between migraine and epilepsy: clinical similarities, pathophysiology mechanisms such as ionic imbalance and cortical spreading depression, prophylactic drugs effective in both diseases and some monogenic syndromes.

Cardiovascular disorders

Migraine and cardiac anomalies with and without right-to-left shunt

A significant amount of attention has recently been placed on the link between patent foramen ovale (PFO) and migraine with aura resulting to be bidirectional. A systematic review conducted by Schwedt et al. on 18 studies showed that the prevalence of PFO in migraineurs ranges from 39.8 to 72.0 %, compared to 25 % in general population (ORs 1.87–5.88). In the other direction, migraine prevalence in patients with PFO ranged from 22.3 to 64.3 % versus a rate of about 13 % in the general population (ORs 1.82–5.88) [18]. Even if this association is epidemiologically evident, its nature is not clear. Fewer studies have investigated other cardiac anomalies related to right-to-left shunts, such as atrial septal defects and pulmonary arteriovenous malformations, and also anomalies unrelated with shunt such as mitral valve prolapse, atrial septal aneurysm and congenital heart diseases [18].

Many studies have investigated the association between migraine and vascular problems showing that migraine, especially MA, is an independent risk factor for ischemic stroke. Nevertheless, the association of migraine and coronary heart diseases is still controversial so results in terms of causal relationships must be interpreted with caution: additional research is needed to establish if migraine is an independent risk factor or related to other cardiovascular risks, if the risk is related to aura status, frequency and intensity of migraine and, lastly, if migraine is per se a modifiable risk factor for Cardiovascular disorders (CVD).

Migraine and other cardiovascular risk factors

Reports on the relationship between migraine and hypertension are controversial and further studies are needed to confirm this association [2]. Obesity is a well-established risk factor for CVD and some studies have investigated its association with migraine. Bigal and colleagues, in a large cross-sectional study, showed that obesity was not associated with increased prevalence of migraine but it was related to headache attack frequency. Conversely, others studies found no association between an increased prevalence of migraine and obesity [2, 19, 20]. Finally, dyslipidemia has also been associated with migraine [2, 19–21].

Migraine and stroke

A systematic review and meta-analysis conducted by Schürks and colleagues investigated the association between any type of migraine and ischemic stroke. They found a pooled relative risk in migraineurs of 1.73 (95 % CI 1.31–2.29) with a higher risk in women than men (2.08 vs. 1.37), in migraineurs with aura than in those without aura (2.16 vs. 1.23), in smokers (9.03) and women using oral contraceptives (7.02) [22, 23]. The Bigal et al. AMPP study confirmed a positive association between migraine and stroke (OR = 1.61) with a significant rate only in those with aura (OR = 3.1) and not in those without (OR = 0.9) [24]. Even if the absolute risk is considerably low because the absolute occurrence of ischemic stroke among migraineurs is rare, these results imply that migraineurs, especially those with aura, should be screened for other traditional cardiovascular risk factors and, if any, checked periodically and treated in order to modify their total risk.

Migraine and sub-clinical vascular brain lesions

Incidental deep brain lesions or sub-clinical infarct-like abnormalities have long been reported as happening more frequently in migraineurs. In a population-based study, Kurth and colleagues compared individuals with MA, with MO and healthy-controls and found no significant difference between migraineurs and controls in overall infarct prevalence (8.1 vs. 5.0 %). However, migraineurs with aura had a higher prevalence of silent infarcts in the cerebellar region of the posterior circulation territory (5.4 vs. 0.7 %, OR = 7.1) compared to controls. Recently, Scher et al. in the AGES-Reykjavik Study evaluated the association between migraine in middle-age and late-life infarct-like lesions showing a stronger linkage between MA and cerebellar lesions in women than men (RR = 1.9) [2, 19].

Other comorbid disorders

Only a few studies have investigated the relation between migraine and others diseases. Fibromyalgia is very common in migraineurs with a prevalence that ranges from 16.8 to 35.6 % and, vice versa, migraine prevalence ranges from 45 to 48 % in fibromyalgia sufferers [25]. Some studies reported a bidirectional association between chronic migraine and chronic fatigue syndrome [2, 26].

The results regarding the linkage between asthma and migraine are contradictory: a large Norwegian epidemiological study showed that both migraine and a specific headache sufferers were approximately 1.5 times more likely among those with current asthma, asthma-related symptoms, hay fever and chronic bronchitis than in those without them and that the association increased with the increase in headache frequency. Another study focusing on the risk of newly diagnosed asthma showed that the relative risk of developing asthma in migraineurs was 1.17 compared with non-migraineurs [2]. Moreover, although the association with irritable bowel disease, endometriosis, celiac disorder and LES has been investigated, further studies are needed to confirm the hypothesis [2, 27–31].

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

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MIGRAINE AS A RISK FACTOR

Migraine and sleep disorders

S. Cevoli · G. Giannini · V. Favoni · G. Pierangeli · P. Cortelli

Abstract The burden of migraine strongly increases, considering its linkage with sleep disorders. Migraine is positively associated with many sleep-complaint disorders; some are confirmed by several studies, such as restless leg syndrome, whereas others still remain uncertain or controversial, e.g. narcolepsy. Many studies have investigated the association between headache and other sleep disturbances such as daytime sleepiness, insomnia, snoring and/or apnea, but only a few have focused on migraine. Highlighting the comorbidity between migraine and sleep disorders is important to improve treatment strategies and to extend the knowledge of migraine pathophysiology.

Keywords Migraine · Sleep · Headache · Parasomnias · Restless leg syndrome

Introduction

Migraine and sleep disorders are prevalent in the general population and are often comorbid in the same subject. The relationship between migraine and sleep has been investigated for a long time: migraine can emerge during nocturnal sleep or following a brief period of daytime sleep; attacks can be preceded by a lack of sleep; sleep has also been shown to relieve migraine, especially in children [1]. Many sleep complaints have been identified to be prevalent in migraineurs: Restless Legs Syndrome (RLS), parasomnias, daytime sleepiness, poor sleep quality and insomnia were the most frequently reported disorders. Migraine was also reported to be more prevalent in narcoleptic patients.

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Migraine and restless leg syndrome

Comorbidity between migraine and RLS has been extensively evaluated in recent years. Rhode et al. [2] in a case–control study on 411 migraineurs and 411 controls, found a significant higher lifetime prevalence of RLS in migraine patients (17.3 vs. 5.6 %, $p < 0.001$, OR 3.5). In addition, they found that migraineurs affected with RLS showed a trend towards worse symptoms of RLS than non-migraineurs. D'Onofrio et al. [3] interviewed and examined 200 patients affected with primary headaches and 120 controls, showing an increase of RLS prevalence in the first group (22.4 vs. 8.3 %, $p = 0.002$). The evaluation of different headache diagnoses showed that migraine without aura can increase the risk of RLS, unlike tension-type headache (TTH) and cluster headache. Similarly, Chen et al. [4] demonstrated that RLS was more common in 772 migraine patients (11.4 %) compared to 218 TTH and 51 cluster headache patients (4.6 and 2.0 %, respectively), highlighting also that migraine patients with RLS had a poorer sleep quality than those without it. Even if two studies have reported a linkage between migraine with aura (MA) and RLS in two different families [5, 6], D'Onofrio et al. [7] have recently remarked that the prevalence of RLS in 63 patients with pure MA was 9.5 %, similar to that observed in Italian headache-free subjects (8.3 %). Finally, Suzuki et al. [8] in a cross-sectional case–control study, compared 262 patients with migraine and 163 headache-free control subjects, confirming higher RLS frequency in the first

group (13.7 vs. 1.8 %) and highlighting that migraineurs with RLS experience more frequently impaired sleep quality, sleep latency and sleep disturbances, use more sleeping medication and have daytime dysfunctions.

Migraine and parasomnias

A higher incidence of parasomnias, among which bruxism, somnambulism, sleep talking and night terror, has been documented in children with migraine compared to controls. At first, Bruni et al [9, 10] found that the rate of night sweating, sleep talking, bruxism, sleep paralysis and nightmares was higher among migraine patients compared with other headaches and control groups. Afterwards, Miller et al. [11] showed that 29 % of children with migraine headaches appeared to have bruxism, whereas the frequency and duration of migraine predicted specific sleep disturbances, including sleep anxiety, parasomnias, and bedtime resistance. A history of somnambulism was present in 32.8 % migraineurs referred to a neurological unit, in comparison with a prevalence of 2–7 % in the general population [12]. In a community sample of students aged 6–13 years, migraine was associated with bedtime struggle, teeth grindings, sleep vocalizations, nightmares, and sleep walking [13]. In a recent population-based survey, the relative risk of all sleep symptoms investigated, except enuresis, was significantly higher in children with migraine; among parasomnias only sleep talking, somnambulism and bruxism were reported [14]. On the contrary, Luc et al. [15] did not find a significant higher prevalence of any parasomnias in a small clinical series of children with migraine. Up to now, sleepwalking and sleep terrors, non-rapid eye movement (NREM) sleep parasomnias, are more prevalent in migraineurs, nevertheless REM parasomnias are less extensively evaluated in migraine patients: only the pioneer study of Bruni et al. [9] reported an association between migraine and sleep paralysis, whereas, hypnagogic hallucination was associated with TTH but not with migraine.

Migraine and narcolepsy

The association between narcolepsy, a disease of REM sleep regulation, and migraine was evaluated in a few hospital-based studies and it is still controversial. After a first observation that half of the narcoleptic patients reported migraine in a clinical sample, Dahmen et al. [16] performed a case–control study in order to evaluate a possible association between migraine and narcolepsy: out of 100 patients suffering from narcolepsy, the migraine prevalence showed a twofold to fourfold increase compared to general population, this data supporting their previous findings. Nevertheless, a contemporary multicenter case–control study obtained different results: in 96 narcoleptics, the prevalence of migraine was of 21.9 % compared to 19.8 % in controls ($p = 0.7$); the prevalence of an unspecific headache, fulfilling the criteria for TTH was however significantly higher in the narcoleptics group [17].

Poor sleep quality, daytime sleepiness, snoring, sleep apnea and migraine

Many studies have investigated the association between headache and other sleep disturbances such as excessive daytime sleepiness (EDS), insomnia, snoring and/or apnea, but only a few have focused on migraine.

Sleepiness is considered a possible migraine symptom that can emerge during various phases of a migraine attack. In a case–control study on 100 patients with episodic migraine and 100 healthy controls, EDS resulted more frequent in the migraineurs group (14 vs. 5 %; OR 3.1, CI 1.1–8.9); EDS is, moreover, correlated with migraine disability, sleep problems and anxiety [18].

Among population-based studies, non-refreshing sleep was found to be more common among migraineurs than the general population (OR 2.98), while migraineous women reported more snoring than women without headache (OR 1.44) [19].

The Third Nord-Trondelag Health Study considered the relationship between sleep disorders, determined by Karolinska Sleep Questionnaire (KSQ) and Epworth Sleepiness Scale (ESS), and headache type and frequency. Migraineurs had a higher prevalence of severe sleep disturbances compared to headache-free persons (OR 5.4, CI 2.0–14.5), and suffered most frequently of EDS than patients with TTH or other headaches and controls (67 vs. 36, 28 and 17 %, respectively). Moreover, the ESS score > 10, considering the cut-off for EDS, was three times more frequent in migraine patients than controls (OR 3.3). There was no difference in the prevalence of snoring and/or sleep apnea among the different headache groups, while insomnia was more frequent in TTH patients than in migraineurs. Finally, the KSQ score in the upper quartile, indicating severe sleep disturbances, was more frequent among subjects with chronic headache (OR 17.4) compared with subjects without headache, and was more evident for chronic migraine than chronic TTH (OR 38.9 vs. 18.3) [20]. A possible relationship between migraine and obstructive sleep apnea in the general population was also denied in a different Norwegian population-based study [21].

Recently, Lateef et al. [22] demonstrated that 5,484 adults suffering from headache reported sleep disorders more than twice (OR 2.8) and three or more insomnia

related complaints (OR 2.5) compared to controls, even though the prevalence of sleep disorders shows no difference in the headache subtypes. Compared to healthy subjects, migraineurs experienced increased difficulty in initiating sleep (OR 2.2), staying asleep (OR 2.8), early morning awakening (OR 2.0) and daytime fatigue (OR 2.6), but no strong differences were reported when comparing migraine with other headaches. Previous results were confirmed by Seidel et al. [23], who reported that the quality of sleep decreased in patients with migraine, whereas fatigue and daytime sleepiness did not differ from controls. Kelman et al. [24] also demonstrated that insomnia symptoms were threefold greater among migraineurs than general population, and that patients suffering from chronic migraine reported shorter nightly sleep than those with episodic migraine, complaining more likely of trouble in falling and staying asleep. In the general Spanish population, migraine was more common in those who sleep less than 8 h/day confirming an association between migraine and poor sleeping [25].

A case–control study showed that chronic headache patients, mainly chronic migraine patients with medication overuse, have a high prevalence of sleep complaints and that these can be an independent risk for headache chronification [26].

In addition, the relationship between headache and sleep complaints in children and adolescents has been widely studied: in an Italian population-based study the most frequent triggering factor for migraine or non-migraine headache was "bad sleep", while the self-perception of disturbed sleep was prevalent in children and adolescents with migraine or other headaches [10].

Many other clinical and population-based studies have investigated the comorbidity between headaches and sleep complaints: taken together the results of these studies, with a few exceptions, confirm the association between migraine and poor sleep quality, while the association between migraine and snoring or sleep apnea is confuted. It is still debated if the comorbidity between sleep complaints and migraine is specific or shared with other headaches.

Conclusion

The relevance of the association between migraine and sleep disorders may be summarized in two considerations: the comorbidity between migraine and specific sleep disturbances may highlight new pathophysiological speculations; moreover, it impacts migraine management. Migraine may share with RLS, parasomnias and narcolepsy, neuroanatomic and neurophysiological mechanisms involving especially the hypothalamus, brainstem nuclei and dopaminergic pathways. Collecting sleep history, diagnosing and treating comorbid insomnia in patients with frequent migraine, and managing sleep related triggers of migraine attacks should become routine care [27].

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

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MIGRAINE AS A RISK FACTOR

Migraine and cardiovascular diseases

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Abstract Migraine has complex relationships with cerebrovascular and cardiovascular disorders but also with cardiac anomalies. Patients affected by migraine with aura have an increased prevalence of right-to-left shunt due to patent foramen ovale or pulmonary arteriovenous malformations. The association between ischemic heart disease, cardiovascular mortality and migraine remains unsettled. The debate focuses on a physiopathological link between migraine and cardiovascular diseases or a higher prevalence of risk factors in migraineurs.

Keywords Migraine · Cardiovascular disease · Right-to-left shunt · Patent foramen ovale · Cardiac anomalies

Introduction

Migraine is primarily a neuronal phenomenon but vascular mechanisms are clearly involved. Several studies have demonstrated that migraine with aura (MA) is a risk factor for ischemic stroke especially in young women [1]. Kruit et al. [2] showed an increased MRI prevalence of subclinical ischemic lesions in the posterior circulation in MA with frequent attacks. The location and patterns of these strokes often suggest an embolic mechanism. This hypothesis has focused attention on the heart as a possible embolic source. Although this topic remains controversial, several studies have demonstrated a role of the right-to-left shunt (RLS) particularly due to patent foramen ovale (PFO). In addition, increasing evidence suggests an association between migraine, myocardial infarction (MI) and cardiovascular disease (CVD)-induced death. The conundrum is whether migraine and CVD are associated or whether migraine is a risk factor especially for coronary heart diseases (CHD). The high prevalence of both migraine and CVD has a substantial impact on public health. We reviewed current evidence on the association between migraine and CVD.

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Migraine and structural cardiac anomalies

Cardiac anomalies with RLS

Significant attention has recently been paid to the link between PFO and migraine being bi-directional. A systematic review by Schwedt et al. on 18 studies showed that the prevalence of PFO in migraineurs ranges from 39.8 to 72.0 % compared to 25 % in the general population. This increased linkage was attributable to MA (40.9–72.0 %) and not without aura (16.2–33.7 %). Compared to controls, patients have an OR ranging from 1.87 to 5.88 with a summary OR of 2.54 (95 % CI 2.01–3.08). In the other direction, migraine prevalence in patients with PFO ranged from 22.3 to 64.3 % versus a rate of about 13 % in the general population. The prevalence of MA ranged from 12.9 to 50 % while the rate of migraine without aura (MO) was weaker (2.8–25 %). The ORs for migraine and PFO ranged from 1.82 to 5.88, with a summary OR of 5.13 (95 % CI 4.67–5.59) that became higher when only MA was considered (summary OR of 3.21, 95 % CI = 2.38–4.17) [3, 4]. Some studies in that review focused on aura status showing that MA patients have an increased risk of PFO

whereas others suggested a relationship between shunt size and prevalence of migraine [3, 4]. Wilmshurst et al. showed that MA was 4.5 times more prevalent in those with a large shunt at rest than in those with no shunt (52.9 compared with 11.8 %) while subjects with a small shunt (at rest or with a Valsalva manoeuvre) have a lower prevalence of MA, similar to those with no shunt [3, 4]. Schwerzmann et al. found out that nearly half of all patients with MA have a PFO and that moderate-sized or large shunt was found more often in the migraine group (38 vs. 8 % in controls; $p < 0.001$) [3, 4]. Fewer studies have investigated other cardiac anomalies related to RLS, such as atrial septal defects (ASDs). Although these are often associated with RLS, the shunting may occur during activities increasing right atrial pressures such as Valsalva [4]. Mortelmans et al. noted that 29.3 % of patients with ASDs had migraine whereas in Azarbal et al. this rate was 30 % [4]. Finally, the linkage between pulmonary arteriovenous malformations (PAVMs) and migraine was analyzed in people with hereditary hemorrhagic telangiectasia because they presented PAVMs in 70 % of cases [4]. Among patients with PAVMs, Thenganatt et al. and Post et al. discovered a prevalence of migraine of 46 % and of 45.2 % (73.4 % of these with MA), respectively [4]. There are several hypotheses [5] on a causal relationship between RLS and MA. The first theory suggests that subclinical emboli and metabolites from the venous system circumvent the lungs and directly enter the systemic circulation. Serotonin is principally metabolized by lung MAO but if a RLS is present some blood avoids the pulmonary circulation and the higher serotonin cerebral plasma levels are postulated to trigger migraine onset. Another mechanism could be a transient hypoxemia causing arterial desaturation and consequent increase in plasminogen activator inhibitor-1 that facilitates hypercoagulability. The role of PFO closure in MA therapy is controversial [4, 5]. To date, the only randomized controlled trial is MIST [6]. The PFO closure and the sham procedure did not show a significant difference in the primary endpoint, i.e., migraine cessation, but migraine frequency was significantly reduced in the closure group ($p = 0.02$). The patients were followed for 3–6 months so a residual effect of aspirin and clopidogrel therapies must be considered. For now, the principal objective is the identification of selection criteria of migraineurs who can benefit from PFO closure considering the risks of this procedure.

Cardiac anomalies without RLS

Some observational studies have suggested a relationship between migraine and mitral valve prolapse (MVP). Litman et al. detected a migraine prevalence of 27.8 % in patients with MVP and, vice versa, Amat et al. found a 25 % prevalence of MVP in migraineurs versus 9.2 % in all headache patients [4]. Spence focused on aura status showing that MA patients had an increased risk of MVP compared to healthy controls (OR = 2.7), whereas Carerj investigated the link between migraine and atrial septal aneurysm noting a 13.3 % prevalence in migraineurs compared to controls (1.9 %) with a risk attributable to those with aura and not to those without 28.5 versus 3.6 %, respectively [4].

Finally, Truong et al. found a 45 % migraine prevalence in adults with congenital heart diseases compared to 11 % in patients with acquired heart diseases ($p < 0.001$). In migraineurs, 80 % had MA and 20 % MO versus 36 and 64 % observed in the control groups ($p < 0.001$). The frequency of migraine was estimated at 52 % in the RLS group, 44 % in the left-to-right and 38 % in the no-shunt group (p:NS). The authors concluded that the higher than expected frequency of migraine in patients with CHD without an intracardiac shunt suggests additional mechanisms to explain the significant association with MA [4].

Migraine and CVD

The association between migraine and CHD is controversial in several large scale population-based studies. The Atherosclerosis Risk in Communities Study evaluated the prevalence of Rose angina and CHD showing that the risk of angina was higher in migraineurs, especially in those with MA (prevalence ratio PR = 3.8 in women and PR = 4.4 in men) versus controls (PR = 1), whereas the risk of CHD did not increase (PR = 4.5 vs. 4.3 in women and PR = 11.5 vs. 13.6 in men) [7]. The Women's Health Study showed that cardiovascular risk was higher in women with MA with an adjusted HR of 2.15 for major CVD, 2.08 for myocardial infarction (MI), 1.74 for coronary revascularization, 1.71 for angina and 2.33 for ischemic cardiovascular death. MO was not linked to CVD [8]. In the Physician's Health Study men with migraine showed an increase in the risk of MI (HR = 1.42) and major CVD (HR = 1.24) after adjustment for cardiovascular risk factors. There was no significant increase in the risk of coronary revascularization, angina or ischemic cardiovascular death [9]. Recently, the AMPP study showed that in both genders migraine was generally associated with MI and claudication. Even if migraineurs compared to controls were most likely to have diabetes, hypertension and high cholesterolemia, these associations were still significant after adjustments, with an OR of 2.16 for MI and 2.69 for claudication. Both associations were further increased in MA compared MO (OR MI = 2.85 vs. 1.85; claudication OR = 4.61 vs. 3.11) [10, 11]. Finally, a systematic review and meta-analysis conducted by Schürks et al. [1] concluded that in migraineurs: (1) an overall

analysis does not suggest an increased risk for MI and only one study, presenting results stratified by migraine aura status, showed a twofold increased association in MA patients, (2) the risk of angina seems to be significantly increased (pooled RR 1.29) with a higher risk in women than in men, in MA than in MO patients, (3) there was no association with death due to CVD (pooled RR 1.03) except for women (RR = 1.60) [1].

Migraine and cardiovascular risk factors

Many studies have investigated the association between migraine and vascular diseases showing that migraine, especially MA, is an independent risk factor for ischemic stroke. Nevertheless, the association of migraine and CHD remains controversial so results in terms of causal relationships must be interpreted with caution. Established cardiovascular risk factors also been linked to migraine include hypertension, obesity, dyslipidemia and pro-inflammatory state. Reports on the relationship between migraine and hypertension are controversial. Recently, two prospective population-based studies demonstrated a negative association between migraine and hypertension showing that migraineurs have low blood pressure [12, 13]. The Women's Health Study confirmed these results demonstrating a similar rate of hypertension in MA, MO and healthy controls although the AMPP study showed higher cholesterol and blood pressure levels in migraineurs compared to controls (32.7 vs. 25.6 %, OR 1.4, 95 % CI 1.3–1.5 and 33.1 vs. 27.5 %, OR 1.4, 95 % CI 1.3–1.6, respectively) [8, 10]. Obesity is a well-established risk factor for CVD and some studies have investigated its association with migraine with controversial results [14]. Bigal and colleagues [15] in a large cross-sectional study showed that obesity was not associated with an increased prevalence of migraine but it was related to headache attack frequency: frequent headache went from 4.4 % in the normal-weight group to 13.4 % in the obese group and 20.7 % in the severely obese group [15]. Further studies conducted by the same authors highlighted that very frequent headaches were significantly more frequent in the obese (8.2 %) and morbidly obese (10.4 %) group, and less in the normal weight group (6.5 %) [16, 17]. Peterlin et al. [18] showed that migraine prevalence increased in adults <55 years old with total body obesity and in women <55 years old with abdominal obesity if compared to adults without them both. Conversely, others studies found no association between increased prevalence of migraine and obesity: Mattssonn [19, 20] showed a proportion of obesity that did not differ between women with active migraine, with inactive migraine or who had never experienced migraine ($p = 0.96$) and Keith et al. [19, 20] confirmed, in a cross-sectional analysis of 11 datasets, that migraine was not related to BMI19 [20]. Ford et al. [21] focused on the intensity of migraine identifying a risk of severe headaches or migraines in participants with BMI >30 compared to subjects with BMI 18–25 (OR = 1.37). Similar results were noted by Winter et al. [22] reporting that women with a BMI <23 kg/m^2 and a BMI ≥35 kg/m^2 had an increased risk of daily migraine, with the highest estimates for the high BMI group. The Women's Health Study also showed that migraine prevalence was higher in those with BMI >35, although this association disappeared after adjustment for cardiovascular factors and postmenopausal status [22]. Finally, dyslipidemia has also been associated with migraine. In the Genetic Epidemiology of Migraine study, compared to controls, migraineurs with aura were more likely to have: (1) an unfavorable cholesterol profile [total cholesterol (TC) ≥240 mg/dL) (OR = 1.43, CI = 0.97–2.1), (2) TC:HDL ratio >5.0 (OR = 1.64, CI = 1.1–2.4), (3) an elevated BP (systolic BP >140 mmHg or diastolic BP >90 mmHg) (OR = 1.76, CI = 1.04–3.0), (4) female migraineurs with aura were more likely to be using oral contraceptives (OR = 2.06, CI = 1.05–4.0). The odds of having an elevated Framingham risk score for CVD were approximately doubled for migraineurs with aura [24]. The Women Health's Study showed that migraine was only weakly associated with elevated TC and elevated levels of C-reactive protein: women with a history of migraine had modestly increased adjusted ORs (95 % CI) of 1.09 (1.01, 1.18) for elevated TC and 1.13 (1.05, 1.22) for CRP. The increase did not differ according to migraine aura status and migraine frequency [23]. Rist et al. [25] found a link between MA and elevated levels of TC and triglycerides in elderly patients: considering the second tertile (5.71–6.49 mmol/l) and third tertile (>6.49 mmol/l) of cholesterol and the third tertile (>1.42 mmol/l) of triglycerides, MA patients had an RR of 4.67, 5.97 and 4.42, respectively, compared to those with other types of severe headaches.

Conclusions

An increased prevalence of PFO and MA exists but data on the causal relationship between these two conditions remain controversial. Issues such as whether screening for PFO is indicated in MA patients and the indications for PFO closure are still unsolved. Firm evidence on the association of migraine and other ischemic vascular events is lacking. Future studies should establish if migraine is an independent cardiovascular risk factor and as a result how to prevent this increased risk.

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

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MIGRAINE AS A RISK FACTOR

Migraine and small vessel diseases

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Abstract It is remarkable that migraine is a prominent part of the phenotype of several genetic vasculopathies affecting small cerebral vessels, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, retinal vasculopathy with cerebral leukodystrophy and hereditary infantile hemiparesis, retinal arteriolar tortuosity and leucoencephalopathy. Moreover, several studies have reported an association between migraine and white matter lesions or clinically silent infarct-like abnormalities in the posterior circulation. In this review, we focus on genetic vasculopathies associated with migraine and speculate about the pathophysiological mechanism that can explain this comorbidity.

Keywords Migraine · Small vessels · Genetic vasculopathies

Introduction

The classical vascular theory that migraine aura is primarily caused by vasoconstriction and migraine headache by vasodilatation is too simplicistic [1]. Part of the current theory is that migraine aura results from cortical spreading depression (CSD) which is a short lasting depolarization of neuronal and glial cell membranes spreading over cortex [2]. Activation of the trigeminovascular system (TGVS) plays a role in migraine headache, leading to the release of vasoactive neuropeptides (CGRP, substance P, NO), which are believed to cause neurogenic inflammation, central pain transmission and headache [2]. In this theory, vasodilatation of cerebral and meningeal vessel is considered a secondary phenomenon that may occur after activation of TGVS. Recent studies, however, have casted considerable doubt about the role of vasodilatation in migraine. For instance, CGRP antagonists do not have a vasoconstrictive effect, but are very effective in the treatment of migraine [3]. In addition, a study using a sensitive 3 Tesla MRA-technique, failed to show in vivo cerebral and meningeal vasodilatation in humans during migraine headache [4]. Nevertheless, this study does not rule out a role for small cerebral vessels. This is relevant because small cerebral vessels are involved in blood flow changes that occur during CSD. Functional neuroimaging studies [5] have shown that the blood flow changes consisted of an initial hyperemia during depolarisation of neuronal and glial membranes, followed by a reduction of cerebral blood flow during hyperpolarization and suppression of neuronal and glial membranes. Changes in blood flow are considered to follow the virtually increased and then reduced metabolic demand of neurons and glial cells during CSD. Recently, it was demonstrated that a reverse order of events, i.e. a vascular event able to trigger CSD, may also be possible [6, 7]. Dreier et al. [6] showed that the vasoconstrictive peptide endothelin-1 (ET-1) induced change characteristic of CSD in the rat cortex, as ET-1 is not capable of inducing CSD in rat brain slices without intact perfusion, it was suggested that a vascular mediated event act as a trigger for CSD. Brennan and co-workers [7] showed that vasomotor changes in the cerebral cortex travel at a significantly greater velocity than the neuronal changes, with a different pattern (circuitous along arterioles as opposed to the

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concentric parenchymal CSD pattern), and dissociated from neuronal changes (it extended beyond the margins of the spread of parenchymal CSD). Thus, although it is generally accepted that during a migraine attack alterations in neuronal activity precede vascular changes, their data suggest that vascular alterations may trigger neuronal dysfunction. The clinical observation that migraine is associated with monogenetic cerebral small vessel diseases further indicates that vascular changes may increase susceptibility to migraine. Here, we discuss in more detail three entities: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), retinal vasculopathy with cerebral leukodystrophy (RVCL) and hereditary infantile hemiparesis, retinal arteriolar tortuosity and leucoencephalopathy (HIHRATL).

Genetic vasculopathies

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is a monogenic disease characterized by middle-age onset of cerebrovascular disease that often progress to dementia. Around 30 % of CADASIL patients are affected by migraine attacks—the majority with aura—often as the first symptom of the disease. CADASIL is caused by mutations in the NOTCH3 gene located on chromosome 19. The NOTCH3 gene encodes for a transmembrane receptor, which is solely expressed in vascular muscle cells in humans. Histopathological findings in CADASIL consist of degeneration of vascular smooth muscle cells with adjacent deposits of granular osmiophilic material and fibrous thickening of the arterial walls. Cerebral magnetic resonance imaging (MRI) reveals characteristic white matter hyperintensities (WMHs) with or without lacunar infarctions and microbleeds [8]. The number, sites and type of lesions are age-dependent. Site of predilection of WMHs are the anterior temporal lobe, the periventricular white matter, external and internal capsule and the pons [9]. The prevalence of migraine in CADASIL ranges from 14 to 72 % in European studies [9–11]. The four studies from Asian countries [12] found a low migraine prevalence of 5 %. When the results are pooled, the overall prevalence of migraine in all CADASIL studies is 38 % with a 95 % CI 33–42 %. The migraine prevalence in CADASIL was higher in females than in males, but this difference did not reach statistical significance [12]. The percentage of migraine with aura could only be inferred from two of the larger study [9, 10], which showed that the majority (80–90 %) of migraneurs with CADASIL have migraine with aura. Vahedi et al. [13] reported that migraine aura in CADASIL is typical in 44 % of cases, while the other 56 % also experience atypical features: aura without headache, hemiplegic auras, basilar-type-migraine symptoms, prolonged aura and acute-onset aura. Vahedi et al. [13] investigated possible associations between MRI abnormalities and migraine in CADASIL and found that MRI findings did not differ between patients with migraine with aura and those without migraine. Moreover, no association was found between migraine and WHMs and lacunar infarcts in pons, occipital lobe and cerebellum. Imaging studies of cerebral hemodynamics in CADASIL reported decreased total cerebral blood flow [14] and decreased cerebral perfusion in normal and abnormal appearing white matter [15]. Also, decreased vasoreactivity was found in areas of WMH.

Retinal vasculopathy with cerebral leukodystrophy is a neurovascular syndrome that primarily involves the retina and the central nervous system [16]. The most prominent symptom is a vascular retinopathy. Neurological manifestations may include cognitive disturbances, depression, migraine (mainly without aura) and focal neurological symptoms. In later disease stages, cerebral MRI scans often show characteristic contrast-enhancing intracerebral mass lesions.

Several systemic symptoms can be present including renal and liver dysfunction, Raynaud's phenomenon and gastro-intestinal bleeding. RCLV is caused by mutation in the TREX1 gene located on chromosome 3. Histopathological examination of cerebral tissue [17] showed white matter necrosis, fibrinoid necrosis, thrombosis of microvessels with perivascular inflammatory infiltrates and reactive gliosis of astroglia. In one of the families, electron microscopic examination showed a multilaminated capillary basement membrane. Because of the other prominent clinical features, especially the retinopathy and intracerebral mass lesions, not much attention was given to the occurrence of migraine in RCLV families. However, in a large Dutch RVCL family ($n = 54$), genetic evidence was obtained that TREX1 might act as a genetic modifier for migraine [18].

Hereditary infantile hemiparesis, retinal arteriolar tortuosity and leucoencephalopathy, a genetic vasculopathy that affects both cerebral and retinal small vessels, is caused by mutations in the COL4A1 gene that is located on chromosome 13. Migraine with aura has been described in a family with HIHRATL carrying COL4A1 mutation G652E [19]. The COL4A1 gene encodes the α1 chain of type IV collagen, a ubiquitous expressed basement membrane protein. Histopathological examination of brain tissue of COL4A1 mutation carriers has not been performed yet. However, in COL4A1 mutant mice, the cerebral vascular basement membrane is affected and present local disruptions, irregular thickening and enlargement of endothelial cells. Of note, in a family with hereditary poroencephaly, carrying a COL4A1 mutation, migraine

without aura was described in one patient, while in two other patients the migraine subtype was not specified [20].

Pathophysiological considerations

CADASIL, RVCL and HIHRATL with COL4A1 mutation have migraine as part of the phenotype and in these conditions the integrity of cerebral and systemic small vessels is affected.

The mechanism by which these vasculopathies can increase the risk of migraine is unknown and different hypothesis can be formulated.

Shared genetic factors

The co-occurrence with migraine may be causally related to certain NOTCH3, TREX1 and COL4A1 mutations. In this case, the genes may be considered to increase the susceptibility for migraine. For the TREX1 gene, a genetic, family-based, association study demonstrated that the RVCL locus slightly enhances the susceptibility for migraine [18]. One study found an association between the NOTCH3 polymorphism G684A and migraine, but this has to be confirmed [21], on the other hand no association was found between the NOTCH3 polymorphism T6746C and migraine [22]. Unfortunately, studies performed thus far have the limitations of small sample size.

Vascular endothelial dysfunction

There is evidence that migraine attacks are associated with endothelial dysfunction. Migraine prevalence is increased in persons with polymorphisms linked to endothelial function [23, 24], moreover, circulating endothelial progenitor cell numbers and function are reduced in migraine patients [25]. In CADASIL and RVCL, pathological changes in endothelial cells may interfere with endothelial function and alter vascular reactivity. Endothelial function has been studied in CADASIL. Mice expressing the mutated protein display early dysfunction in vasoreactivity with decreased flow-induced dilatation and increased pressure-induced myogenic tone. In CADASIL patients, impaired endothelial function was also found in two studies [26, 27].

Neuronal mechanism

Cortical spreading depression is considered the underlying mechanism of the migraine aura. A hypothesis for the increased prevalence of MA in CADASIL could be that vascular changes make the cortex more susceptible to CSD, thereby increasing the risk for MA. Indeed in CADASIL patients, a reduced cerebral baseline flow [27], a decreased cerebrovascular reactivity [14, 15] and an impaired endothelial function [26, 27] were demonstrated. Furthermore, it was recently shown that vasomotor changes can precede neuronal dysfunction [7] and that a vascular event, such as a clinical insignificant ischemia, is able to trigger CSD [6]. These observations strengthen this hypothesis for CADASIL. Increased susceptibility for CSD seems a less plausible mechanism for RVCL, as this syndrome is mainly associated with MO. However, it could also form an explanation for the occurrence of MA in three out of six family members with HIHRATL.

Besides these genetic vasculopathies patients with migraine often present on brain MRI white matter lesions that resemble ischemic infarcts in the territory of small cerebral vessel. The CAMERA study [28] suggests that patients affected by migraine are independently at increased risk for subclinical brain lesions, in particular in the posterior circulation. This was evident only among patient affected by migraine with aura and particularly for those with at least 12 migraine episodes for year. In a recent study, migraine with aura in midlife correlates in women with late-life prevalence of cerebellar infarct-like lesions on MRI. These data persisted after controlling for cardiovascular risk factors and history of cardiovascular disease [29]. The cause and mechanisms of white matter lesions remain subject to debate. Prolonged and repeated oligemia during migraine attacks may affect the vulnerable small deep penetrating arteries, and local critical hypoperfusion may lead to minor brain injury revealed as white matter lesions. Other proposed mechanisms include atherosclerotic causes including common cardiovascular risk factors, endothelial dysfunction, shared genetic risk factors for migraine and stroke, medications with vasoconstrictor activity and cardiac abnormalities including patent foramen ovale.

Conclusion

In genetic small vessel diseases, vascular changes including endothelial dysfunction, may directly or via neuronal pathways increase the risk for migraine. Alternatively, DNA variants in the susceptibility genes may directly form a risk factor for migraine and the syndrome itself. For genetic as well as acquired vasculopathies, research into endothelial function and shared genetic factors will be important to understand the pathophysiological mechanisms that can explain their comorbidity with migraine.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

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MIGRAINE AS A RISK FACTOR

Migraine and movement disorders

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Abstract A large series of clinical and experimental observations on the interactions between migraine and the extrapyramidal system are available. Some previous studies reported high frequency of migraine in some basal ganglia (BG) disorders, such as essential tremor (ET), Tourette's syndrome (TS), Sydenham's chorea and more recently restless legs syndrome (RLS). For example, the frequency of migraine headache in a clinic sample of TS patients was found nearly fourfold more than that reported in the general population. To the best of our knowledge, no controlled studies have been conducted to determine a real association. ET and migraine headache have been considered comorbid diseases on the basis of uncontrolled studies for many years. In a recent Italian study, this comorbid association has been excluded, reporting no significant differences in the frequency of lifetime and current migraine between patients with ET and controls. Among mostly common movement disorders, RLS has been recently considered as possibly comorbid with migraine. Studies in selected patient groups strongly suggest that RLS is more common in migraine patients than in control populations, although no population-based study of the coincidence of migraine and RLS has yet been identified. The exact mechanisms and contributing factors for a positive association between migraine and RLS remain unclear. A number of possible explanations have been offered for the association of RLS and primary headache, but the three most attractive ones are a hypothetical dopaminergic dysfunction and dysfunctional brain iron metabolism, a possible genetic linkage and a sleep disturbance. More recently, the role of BG in pain processing has been confirmed by functional imaging data in the caudate, putamen and pallidum in migraine patients. A critical appraisal of all these clinical and experimental data suggests that the extrapyramidal system is somehow related to migraine. Although the primary involvement of extrapyramidal system in the pathophysiology of migraine cannot as yet be proven, a more general role in the processing of nociceptive information and/or maybe part of the complex behavioral adaptive response that characterizes migraine may be suggested.

Keywords Migraine · Restless legs syndrome · Extrapyramidal system · Basal ganglia · Movement disorders

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Introduction

In the last decade, multiple changes in brain functions and sometimes in brain structures as a result of migraine attacks have been described from imaging studies in migraineurs. The more frequently demonstrated brain abnormalities are enhanced cortical excitability [1], altered gray matter

volume in some regions [2, 3], enhanced brain blood flow [4–6] and altered pain modulatory systems [7–9]. Functional imaging studies such as functional MRI and PET and volumetric MRI (voxel-based morphometry) suggested the involvement of pain processing cortical cerebral areas such as cingulated gyrus, anterior insula and medial and lateral prefrontal cortices, both in episodic and chronic migraine patients [10]. Basal ganglia (BG), which receives inputs from thalamus and all cortical regions projecting back to the BG, mostly through BG-thalamo-cortical loops, seems to be involved in the sensory, emotional and cognitive integration of pain information between cortical and thalamic regions [11–13]. Brain imaging studies have shown decreased activation in the BG of migraineurs versus controls in the interictal period [14], increased activation (blood flow) during the ictal state and other non specific lesions [15, 16]. More recently, significant differences in gray matter volume and function in response to pain have been observed interictally in the BG in migraineurs with higher frequency of attacks versus those with lower frequency [17]. A large series of clinical observations on the interactions between migraine and the extrapyramidal system are also available. "Movement" or "motion" influences headache pain, "hypokinetic behavior" characterizes migraineurs and "restless behavior" is a hallmark in cluster patients. Previous studies reported high frequency of migraine in some BG disorders, such as Parkinson's disease (PD), essential tremor (ET), Tourette's syndrome (TS), Sydenham's chorea (SC) and more recently restless legs syndrome (RLS). This review will critically analyze evidences and suggestions available over time, especially in the last decade, on the correlations between migraine and movement disorders, exploring some possible relationships with the aim of obtaining more specific therapeutic approaches.

Methods

Evidences were searched from the medical databases Ovid, PubMed and NHS by combining the key terms migraine, extrapyramidal system, BG, PD, RLS, ET and chorea. Electronic searches were supplemented by hand searching the bibliographies of relevant articles. All authors read the title and abstract of all studies identified by the electronic searches and agreed on the eligibility of the studies identified, the full text of which was read and critically appraised.

Is there a link between migraine and movement disorders?

Numerous descriptions of migraine occurrence in some movement disorders are available in literature. We report the most significant (consistent) ones in favor of a suggestive link between migraine and BG-related disorders.

Parkinson's disease

The lifetime prevalence of migraine in PD ranges from 19.3 to 27.8 % in case–control studies [18, 19]. PD also seems to shorten migraine evolution as suggested in a large cross-sectional study [18]. Nearly two-thirds of PD patients had an improvement in or remission of migraine after PD onset, with a lower frequency of current migraine than healthy controls.

Essential tremor

In the early 90s, uncontrolled studies demonstrated a bidirectional association between ET and migraine, suggesting that the two diseases shared some pathophysiological mechanisms [20, 21] and considering ET to be comorbid with migraine for many years [22]. However, given the high prevalence of both conditions [23, 24], ET and migraine may coexist merely by chance. Duval et al. [25] found no differences in the characteristics of tremor in migraineurs and healthy controls. More coherence about this point was only recently found from the case–control study of Barbanti et al. [26], where a large population of patients with ET and healthy control subjects were enrolled and a similar frequency of lifetime or current migraine in both groups was found. Nevertheless, when migraine and ET coexisted, neither condition influenced the other and their clinical phenotype and evolution remained substantially unchanged.

Tourette's syndrome

Tourette's syndrome is recognized as one of the most common childhood movement disorders, characterized by motor and phonic tics often associated with neurobehavioral comorbidities, such as obsessive–compulsive disorder. Few studies have reported about the prevalence of TS in migraine patients. Kwak et al. [27] confirmed the results of Barabas et al.'s study on childhood [28] and reported that the frequency of migraine in patients with TS was fourfold higher than in the general population (25.0 with 39 % of adults and 16 % of children with TS), regardless of the presence of an obsessive–compulsive trait. The authors conclude that the co-occurrence of migraine might be attributable to another TS comorbidity and that the presence of migraine in family members of patients with

TS "may be used as a clinical marker for this complex genetic disorder".

The high frequency of migraine in patients with TS may be due not only to an aminergic involvement or genetic or psychiatric comorbidities, but also to a disturbance in the BG–thalamocortical circuitry which is involved in the processing of nociceptive information [29].

Sydenham's chorea

Teixeira et al. [30] compared the frequency of migraine among SC patients, rheumatic fever (RF) patients without neurological symptoms and matched controls. Migraine was more frequent in SC patients (21.8 %) than in controls (8.1 %) and as common as in the RF group (18.2 %).

Interestingly [31], a case of a 57-year-old woman with a long history of migraine who suddenly experienced concurrent scintillating scotoma and rapid involuntary movement of her neck and right extremities has been reported. She completely recovered in 15 days, without ischemic and/or hemorrhagic lesions at diffusion-weighted magnetic resonance imaging. Xenon-computed tomography (CT) disclosed gross reduction in the cerebral blood flow (CBF) of the left occipital area, extreme hyperperfusion in the motor left thalamus and asymmetrical CBF reduction of the left subthalamic nucleus. After recovery, repeated xenon-CT 1 month post-onset demonstrated normalized CBF in the affected areas.

Other movement disorders

Among movement disorders, dystonia has been indicated as associated with headache, especially migraine [32]. Starting from this background, Barbanti et al. [33] found that the frequency of headache attributed to craniocervical dystonia (CCD), as listed by ICHD-II classification, was lower than that expected in subjects who have hyperactivity of cervical or cranial muscles or both. The various types of headache investigated had a similar frequency in patients with CCD and healthy controls, supporting that headache attributable to CCD, as diagnosed according to the current criteria, emerged as an infrequent event. Hence, despite causing local muscular pain, in most patients, the dystonic muscular contractions apparently neither trigger nor worsen possible coexisting head pain. It is noteworthy to remind among rare movement disorders, palatal myoclonus, which likely involves some of the same pathogenetic mechanisms of migraine. The reported efficacy of sumatriptan in some cases of palatal myoclonus, the first of them it has been reported by Jankovic et al. [34], support this observation.

Restless legs syndrome

Studies in selected patient groups strongly suggest that RLS is more common in migraine patients than in control populations. However, a population-based study, perhaps the most definitive way to establish concurrence, is yet to be reported. In the Young study [35], with a small sample of patients without the control group, the RLS prevalence rate reported was higher than that expected considering RLS prevalence in the general populations, and this first data has been largely confirmed by subsequent studies. Rhode et al. [36] performed a case control study on 411 patients with migraine with 411 age- and sex-matched control subjects and found that the former had a statistically significant higher lifetime prevalence of RLS than the control group (17.3 vs. 5.6 %, $P = 0.001$). Migraine patients with RLS tended to be older than those without RLS, in keeping with the epidemiological finding that RLS incidence typically increases with age. In our first observational study [37], we conducted interviews and neurological examinations in 200 patients affected by primary headaches and in 120 age- and sex-matched controls. We reported an increased RLS prevalence in headache patients compared to control subjects (22.4 vs. 8.3 %, $P = 0.002$), with a preponderance in patients who suffered from migraine without aura. Chen et al**.** [38] compared the prevalence of RLS between different primary headache groups, without the control group. They found that RLS was more common in migraine patients (11.4 %) than in TTH (4.6 %) and CH (2.0 %) ($P = 0.002$). The lower frequency of RLS in this population compared to the three previously mentioned studies [35–37] suggested that an ethnic factor might contribute to RLS prevalence. The frequency of RLS increased with increasing number of migrainous symptoms (linear by linear association, $P = 0.001$). Among these, sleep disturbances were more frequent in headache patients with RLS (50.0 vs. 32.7 %, $P = 0.001$) [37]. Interestingly, we reported the prevalence of RLS also in pure migraine with aura (pMA) patients to be 9.5 % [39], similar to that observed in Italian headache-free subjects (8.3 %) with no significant differences between pMA patients with and without RLS on clinical features of MA attacks and systemic and psychiatric diseases investigated. Moreover, no association appeared between RLS and familial cases of MA. Differently from migraine without aura, our data do not confirm the existence of an association between RLS and MA, not even when a genetic factor is involved.

Discussion

Migraine has been widely investigated in some movement disorders for the possible role of the extrapyramidal system

in the processing and modulation of pain and in nociceptive sensorimotor integration. Moreover, clinical signs suggestive of extrapyramidal involvement may spontaneously occur in migraine patients.

We discuss evidences, some of them consistent, of a possible association between migraine and movement disorders. Case–control studies have supplied the most reliable results. No associations were found between ET and migraine suggesting that these disorders could not arise from similar pathophysiological mechanisms [26]. Migraine prevalence has been reported to be increased in TS [27] and SC [30], reduced in PD [18, 19], similar to the general population in craniocervical dystonia [33]. The high prevalence of migraine in TS and SC patients has been explained by the involvement of a serotonin system dysregulation, also implicated in the pathogenesis of TS and obsessive–compulsive disorder. It is more difficult to explain the high frequency of migraine in SC, if we also consider the recent observation of a case of motor migraine aura, sustained by a vascular event, with a consequent loss of inhibitory control of the motor thalamus resulting in the manifestation of hemichorea [31]. The reduced frequency of migraine in PD might be due to increased inhibitory activity of the substantia nigra pars reticulate on the thalamus with decreased pain sensitivity observed in PD patients and likely to the anti-migraine properties of drugs used in PD therapy. This intriguing observation likely has a low practice value, because PD is a neurological disorder more common in old ages when migraine leans toward spontaneous remission. The strongest association is between migraine and RLS, which allows making suggestions about possible shared pathogenetic mechanisms, although no population-based study has yet been addressed. Dopaminergic dysfunction and dysfunctional brain iron metabolism are the most postulated mechanisms. Especially for the former, consistent improvement in RLS symptoms with dopamine agonist drugs licensed for RLS treatment and increased incidence of RLS in migraineurs with co-existing dopaminergic symptoms during migraine attacks as we reported [40] are valid arguments in favor of this hypothesis. Other speculations on a joint origin of RLS and migraine such as iron dysmetabolism, well recognized in RLS and migraine patients, a common genetic linkage mapped to chromosome 14q21, as recently described in an Italian family, and sleep disturbances have been well described in a recent review on this topic [41].

On comparing the results of all these studies, case–control, observational and case reports, a wide discrepancy of results emerges, perhaps due to methodological designs and limits such as the lack of a prospective population-based study, the artefacts due to recall bias in clinical studies and finally the size of the sample investigated. The frequency of migraine in different movement disorders seems to drive in different directions (increased in TS, normal in ET, reduced in PD), so the most relevant clinical data become the evidence of strictly the link between motor activities of BG circuitry and pain processing, such as it occurs in migraine.

Besides these clinical findings, imaging studies have indicated that some areas of the extrapyramidal system are likely implicated in migraine [19]. The substantia nigra and red nucleus, for example, are activated during both episodic and chronic migraine. The cerebellum reveals a high expression of the alpha-1 subunit of the P/Q calcium channels, which are involved in the pathogenesis of familial hemiplegic migraine and probably in more common forms of migraine as well. Moreover, extrapyramidal symptoms such as postural and kinetic tremor are more frequent in patients with migraine than controls. Finally, some antimigraine drugs may affect BG motor function.

In the era of functional and morphometric neuroimaging, it seems to be more suitable to address BG than the extrapyramidal system. The BG receives inputs from all cortical regions and the thalamus, and the efferent pathways project, mostly through BG-thalamo-cortical loops, back to the BG [11–13]. This cortical loop has been involved not only in the modulation of BG function during migraine attack or in the interictal period, but also in modifying the course of migraine. If in the near future we can easily measure the BG abnormalities in migraineurs with neuroimaging, we could predict its progression, signaling which episodic patients will become chronic. For clinicians, the recognition of the correlations between a movements disorder, especially TS, SC or more commonly RLS, and migraine will be more fast, convenient and handy than a neuroradiologic finding to identify which patient would progress or not to a chronic form. To have reliable and consistent data, we hope to design large population studies on different movement disorders to better define the role of the extrapyramidal circuitries in headache patients.

To date, we can certainly assume that BG has a role in the pathophysiology of some chronic pain disorders and in particular in migraine, where dopamine and likely other biochemical abnormalities support different clinical phenotypes. These contributions are needed to suggest not only new therapeutic perspectives, but also as predictive parameters for migraine evolution over time.

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

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Frovatriptan versus zolmitriptan for the acute treatment of migraine with aura: a subgroup analysis of a double-blind, randomized, multicenter, Italian study

Vincenzo Tullo · Gianni Allais · Marcella Curone · Michel D. Ferrari · Stefano Omboni · Chiara Benedetto · Bruno Colombo · Dario Zava · Gennaro Bussone

Abstract Migraine with aura affects ~20–30 % of migraineurs and it is much less common than migraine without aura. The aim of this study was to compare the efficacy of frovatriptan 2.5 mg and zolmitriptan 2.5 mg in the treatment of migraine with aura. Analysis was carried out in a subset of 18 subjects with migraine with aura (HIS criteria) out of the 107 enrolled in a multicenter, randomized, double-blind, cross-over study. According to the study design, each patient had to treat three episodes of migraine in no more than 3 months with one drug, before switching to the other treatment. The rate of pain-free episodes at 2 h was significantly ($p < 0.05$) larger under frovatriptan (45.8 %) than under zolmitriptan (16.7 %). Pain free at 4 h, pain relief at 2 and 4 h and recurrent episodes were similar between the two treatments, while sustained pain-free episode was significantly ($p < 0.05$) more frequent during frovatriptan treatment (33.3 vs. 8.3 % zolmitriptan). Our study suggests that frovatriptan is superior to zolmitriptan in the immediate treatment of patients with migraine with aura, and it is capable of maintaining its acute analgesic effect over 48 h.

Keywords Migraine with aura · Frovatriptan · Zolmitriptan

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Introduction

Approximately 20–30 % of people suffering from migraine headaches perceive an aura, namely a transient visual, sensory, language, or motor disturbance signaling the imminent occurrence of a migraine attack [1].

Though migraine with aura shares frequently the same clinical features with respect to the headache of migraine without aura, nevertheless the auras can cause anxiety and distress in the patient, being particularly disabling [2].

Triptans are generally considered the most effective acute treatment for migraine [3, 4]. However, pharmacological trials usually include mixed population of patients or predominantly migraineurs without aura, and do not specifically address drug efficacy in patients with aura [5].

To bring new evidence supporting the efficacy of triptans also in patients with migraine with aura, we analyzed a subgroup of such patients, included in a large randomized, double-blind, cross-over, comparative study of frovatriptan versus zolmitriptan [7].

Methods

Study population

Male or female subjects, aged 18–65 years, with a current history of migraine with or without aura, according to IHS criteria, and with at least one migraine attack per month for 6 months prior to entering the study, were eligible for participation in the main study [6, 7].

Details on study design and inclusion and exclusion criteria are available elsewhere [6]. In this analysis migraineurs with aura were selected. This condition was defined according to IHS criteria as at least two migraine attacks with aura symptoms, consisting of visual and/or sensory and/or speech symptoms [7].

Study design

The study had a multicenter, randomized, double blind, cross-over design and has been extensively described in a previous publication [6]. Briefly, each patient received frovatriptan 2.5 mg or zolmitriptan 2.5 mg in a randomized sequence. After treating a maximum of three episodes of migraine in no more than 3 months with the first treatment, the patient had to switch to the other treatment and asked to treat a maximum of three episodes of migraine in no more than 3 months with the second treatment.

The study involved three visits and each patient's participation time in the study did not exceed 6 months from randomization. Subjects having no migraine episodes during one of the two observation periods were excluded from the study.

Randomization was done by blocks of 4. Blindness was ensured by the over-encapsulation technique, i.e., by inserting study drug tablets in capsules.

Data analysis

The present analysis was carried out in the subgroup of patients with migraine with aura, who actually treated at least one attack in each treatment period. Study endpoints were [7] (a) pain-free episode at 2 and 4 h (absence of migraine 2 and 4 h after intake of one dose of study drug and without any rescue medication); (b) pain relief at 2 and 4 h (defined as a decrease in migraine intensity from severe or moderate to mild or none at 2 and 4 h); (c) recurrence (pain free at 2 h and headache of any severity returning within 48 h); and (d) sustained pain-free episode within 48 h (migraine attack which is pain free at 2 h, does not recur and does not require the use of rescue medication or a second study drug dose within 48 h).

Continuous variables were summarized by the calculation of average values and standard deviation (SD), while categorical variables by computing the absolute value and the frequency (as percentage). Endpoints were compared between groups by generalized estimating equation analysis. The level of statistical significance was set at 0.05.

Results

The whole intention-to-treat population consisted of 107 patients, of whom 18 (16.8 %) had migraine with aura and 89 (83.2 %) had migraine without aura. No statistically significant difference was observed between the two subgroups of patients for baseline characteristics Table 1.

In the 18 patients suffering from migraine with aura, a total of 48 headache attacks were reported: 24 treated with frovatriptan (7.9 % of overall 304 episodes treated with this drug) and 24 treated with zolmitriptan (8.0 % of the overall 299 episodes).

Table 1 Baseline demographic and clinical data of the migraine patients with and without aura of the ITT population

	Migraine with aura ($n = 18$)	Migraine without aura ($n = 89$)	p
Age (years, means ± SD)	38.3 ± 6.1	38.1 ± 10.5	NS
Females (n, %)	16 (88.9)	69 (77.5)	NS
Height (cm, means ± SD)	164.2 ± 5.7	166.2 ± 8.3	NS
Weight (kg, means ± SD)	61.1 ± 6.7	63.7 ± 12.2	NS
Age at onset of migraine (years, means ± SD)	16.5 ± 9.6	16.3 ± 5.7	NS
Migraine attack duration >2 days (n, %)	3 (16.7)	14 (15.7)	NS
MIDAS score (means ± SD)	21.6 ± 14.3	22.8 ± 16.1	NS
No use of triptans in the previous 3 months (n, %)	8 (44.4)	22 (24.7)	NS
Patients with moderate attacks (n, %)	11 (61.1)	49 (55.1)	NS
Patients with severe attacks (n, %)	7 (38.9)	40 (44.9)	NS

Data are shown as mean (±SD), or absolute (n) and relative frequency (%). P refers to the statistical significance of the between-group differences

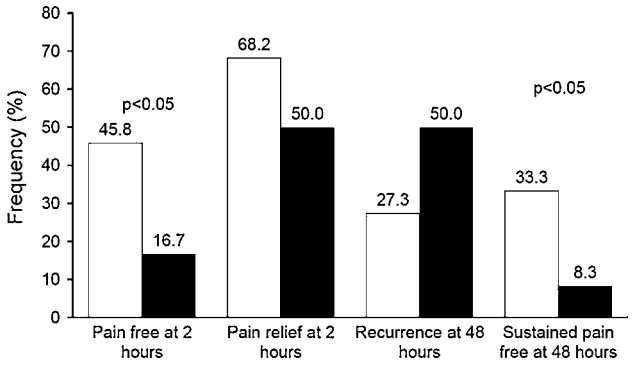

Fig. 1 Rate of pain free at 2 h, pain relief at 2 h, recurrence at 48 h and sustained pain-free episode at 48 h in patients with migraine with aura treated with frovatriptan (*open bars*) or zolmitriptan (*full bars*). Data are shown as relative frequencies (%). *P* refers to the statistical significance of the between-treatment differences

As shown in Fig. 1, rate of pain-free episodes at 2 h was significantly ($p < 0.05$) larger under frovatriptan (45.8 %) than under zolmitriptan (16.7 %). Conversely, pain-free patients at 4 h were equally distributed between the two treatment groups (58.3 % for frovatriptan and zolmitriptan, $p = \text{NS}$). Proportions of patients with pain relief at 2 and 4 h and with recurrences did not significantly differ between frovatriptan (68.2, 72.7 and 27.3 %) and zolmitriptan (50.0, 63.6 and 50.0 %). Sustained pain-free episode was reported significantly ($p < 0.05$) more frequently during frovatriptan treatment (33.3 vs. 8.3 % zolmitriptan, Fig. 1).

Discussion

In this study, we aimed at specifically comparing efficacy of two triptans in migraine patients with aura through a subgroup analysis of an original randomized, double-blind, cross-over study [6]. Treatment with frovatriptan 2.5 mg resulted in almost half of the patients free from pain at 2 h and more than one-third showing sustained pain-free episode at 48 h, with proportions larger than those observed under zolmitriptan. These results may have interesting clinical implications.

To our knowledge, this is the first direct head-to-head comparative study of two triptans in patients experiencing migraine with aura and strictly applying IHS criteria for definition of study endpoints. Although there are no previous studies specifically comparing the efficacy of frovatriptan and zolmitriptan in migraine with aura, our results are in line with those of previous randomized trials or meta-analyses which also included a small sample of migraineurs with aura and are also in line with the results obtained in migraineurs without aura [8–11].

In conclusion, results of our multicenter, randomized, double-blind trial support the indication of frovatriptan also for the management of the acute attack of migraine with aura. In this regard, frovatriptan seems to be superior to zolmitriptan, though future well-designed large-scale studies are needed to reinforce our observation, derived from a limited sample of subjects retrospectively analyzed.

Acknowledgments The present study was supported by Istituto Lusofarmaco d'Italia.

Conflict of interest All authors have occasionally served as scientific consultants for manufacturers of frovatriptan or zolmitriptan. D. Zava is an employee of Istituto Lusofarmaco d'Italia.

Appendix: List of study sites

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SYMPOSIUM: OPEN QUESTIONS ON MIGRAINE

Efficacy of frovatriptan versus other triptans in the acute treatment of menstrual migraine: pooled analysis of three double-blind, randomized, crossover, multicenter studies

Gianni Allais · Vincenzo Tullo · Stefano Omboni · Chiara Benedetto · Grazia Sances · Dario Zava · Michel D. Ferrari · Gennaro Bussone

Abstract The objective of this study was to review the efficacy and safety of frovatriptan (F) versus rizatriptan (R), zolmitriptan (Z) and almotriptan (A), in women with menstrually related migraine (IHS criteria) through a pooled analysis of three individual studies. Subjects with a history of migraine with or without aura were randomized to F 2.5 mg or R 10 mg (study 1), F or Z 2.5 mg (study 2), and F or A 12.5 mg (study 3). The studies had an identical multicenter, randomized, double-blind, crossover design. After treating three episodes of migraine in no more than 3 months with the first treatment, patients had to switch to the next treatment for other 3 months. 346 subjects formed intention-to-treat population of the main study; 280 of them were of a female gender, 256 had regular menses and 187 were included in the menstrual migraine subgroup analysis. Rate of pain free at 2, 4 and 24 h was 23, 52 and 67 % with F and 30, 61 and 66 % with comparators (P = NS). Pain relief episodes at 2, 4 and 24 h were 37, 60 and 66 % for F and 43, 55 and 61 % for comparators (P = NS). Rate of recurrence was significantly ($P < 0.05$) lower under F either at 24 h (11 vs. 24 % comparators) or at 48 h (15 vs. 26 % comparators). Number of menstrual migraine attacks associated with drug-related adverse events was equally low (P = NS) between F (5 %) and comparators (4 %).

Keywords Almotriptan · Menstrually related migraine · Frovatriptan · Rizatriptan · Zolmitriptan

The members of coordinators and investigators are listed in Appendix.

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Introduction

In more than 50 % of women with migraine, the migraine attack is often associated with the menstrual cycle [1, 2]. These headache attacks are reported to be particularly severe, more disabling, more difficult to manage, and need immediate acute or preventive treatment with a drug capable of ensuring a sustained effect [3].

The efficacy and safety of triptans in the management of menstrual migraine, either as acute therapy or intermittent prophylaxis, have been demonstrated in numerous randomized clinical trials [4]. Following this evidence, these drugs are now recommended as first-line treatment for menstrual migraine [5, 6].

Frovatriptan is an antimigraine agent of the triptan class developed in order to provide a triptan with the clinical potential for a long duration of action and a low likelihood

of side effects and drug interactions [7]. Recently, post hoc analyses of three double-blind, randomized, crossover, head-to-head trials have compared the efficacy and safety of frovatriptan with that of rizatriptan [8], zolmitriptan [9] and almotriptan [10] in women with menstrual migraine. These studies showed a similar efficacy of frovatriptan, rizatriptan, zolmitriptan and almotriptan in the immediate treatment of menstrual migraine, but lower recurrence rates, and thus a better sustained relief under frovatriptan.

In the present paper, we report on results of a pooled efficacy and safety analysis of frovatriptan versus the comparators in menstruating women based on the aforementioned publications.

Methods

Study population and design

The original study design of the three studies, including patient's selection criteria, is detailed in the original publications [8–10]. Briefly, the studies recruited subjects of both genders, aged 18–65 years, with a current history of migraine with or without aura, according to the International Headache Society definition [11], and with at least one, but no more than 6 migraine attacks per month for 6 months prior to entering the study. The analysis of this subgroup population was predefined in the statistical analysis plan and original protocols of the three studies. This condition was defined according to the IHS research criteria, as migraine without aura attacks in a menstruating woman, occurring on day 1 ± 2 (namely days -2 to $+3$) of menses in at least two out of three menstrual cycles and additionally at other times of the cycle [11].

The studies had a multicenter, randomized, double-blind, crossover design and involved 33 different centers across Italy. Each patient received frovatriptan 2.5 mg or rizatriptan 10 mg in the first study [8], frovatriptan 2.5 mg or zolmitriptan 2.5 mg in the second study [9] and frovatriptan 2.5 mg or almotriptan 12.5 mg in the third study [10] in a randomized sequence. After treating a maximum of three episodes of migraine in no more than 3 months with the first treatment, the patient switched to the other treatment and was asked to treat a maximum of three episodes of migraine in no more than 3 months with the second treatment.

The study involved three visits and each patient's participation time in the study was not to exceed 6 months from randomization. Subjects having no migraine episodes during one of the two observation periods were excluded from the study.

Randomization was done by blocks of four. Blindness was ensured by the overencapsulation technique, i.e., by inserting study drug tablets in capsules.

Data analysis

This pooled analysis was carried out in all menstruating women randomized to any of the two treatment sequences foreseen in each study, enrolled to receive either study treatment and having treated at least one episode of menstrual migraine with both medications in each study.

The following endpoints were evaluated [11]: (a) the proportion of pain relief episodes at 2, 4 and 24 h (a decrease in migraine intensity from severe or moderate to mild or none at 2, 4 and 24 h); (b) the proportion of pain free episodes at 2, 4 and 24 h (the absence of migraine episodes at 2, 4 and 24 h after intake of one dose of study drug); (c) recurrence within 24 h (episodes pain free at 2 h and headache of any severity returns within 24 h); (d) recurrence within 48 h.

Safety analysis was applied to the intention-to-treat population, by calculating the incidence of drug-related adverse events.

Continuous variables were summarized by computing average values and standard deviations (SD), while categorical variables by computing the absolute value and the frequency (as percentage). Study endpoints were compared between groups by a *t* test of Student (continuous variables) or by a Chi-square test (categorical variables). Kaplan–Meier curves for the cumulative hazard of recurrence over the 48 h were also drawn. The level of statistical significance was kept at 0.05 for all analyses.

Results

Baseline demographic and clinical data

The main study population consisted of 346 subjects, of whom 280 were women and 236 in the fertile age [8–10]. A total of 187 out of the 236 eligible women treated at least one episode of menstrual migraine with both medications and were thus included in the present analysis.

Demographic and clinical baseline data of the 346 patients of the three main studies pooled together and of the subgroup of 187 women with menstrually related migraine are reported in Table 1. No statistically significant differences were observed between the whole study population and the subgroup.

Efficacy results

A total of 401 out of the overall 1,978 attacks were classified as menstrually related: 199 (20 %) were treated with frovatriptan and 202 (20 %) with comparators (66 women treated with rizatriptan, 54 with zolmitriptan and 67 with almotriptan).

As summarized in Table 2, at 2, 4 and 24 h the rates of pain relief episodes were not significantly ($P = \text{NS}$)

Table 1 Demographic and clinical baseline data of the 346 patients of the three main studies pooled together and of the subgroup of 187 women with menstrually related migraine

	Main studies ($n = 346$)	Subgroup of menstruating women ($n = 187$)	P
Age (years, mean ± SD)	38 ± 10	36 ± 8	NS
Height (cm, mean ± SD)	166 ± 7	164 ± 6	NS
Weight (kg, mean ± SD)	64 ± 13	61 ± 9	NS
Age at onset of migraine (years, mean ± SD)	17 ± 7	16 ± 6	NS
Migraine attack duration >2 days (n, %)	72 (21)	42 (22)	NS
No use of triptans in the previous 3 months (n, %)	146 (42)	83 (44)	NS
Moderate or severe attacks (n, %)[a]	1,574 (80)	327 (82)	NS
Patients with at least one moderate or severe attack (n, %)	334 (97)	179 (96)	NS

Data are shown as mean (±SD) or absolute (n) and relative frequency (%)

[a] Numbers refer to number and frequency of attacks with respect to overall number of attacks

Table 2 Main study endpoints in the two study treatment groups (frovatriptan and other triptans)

	Frovatriptan	Comparators	P
Pain relief episodes at 2 h	74 (37)	87 (43)	NS
Pain free episodes at 2 h	46 (23)	60 (30)	NS
Pain relief episodes at 4 h	120 (60)	113 (55)	NS
Pain free episodes at 4 h	104 (52)	124 (61)	NS
Pain relief episodes at 24 h	133 (66)	124 (61)	NS
Pain free episodes at 24 h	133 (67)	133 (66)	NS
Recurrent episodes at 24 h	22 (11)	49 (24)	<0.05
Recurrent episodes at 48 h	29 (15)	53 (26)	<0.05

Data are reported as absolute (n) and relative (%) frequency. P refers to the statistical significance of the difference between the two study drugs

different between frovatriptan (37, 60 and 66 %) and the comparators (43, 55 and 61 %, respectively). Also, the proportions of pain free episodes at 2, 4 and 24 h did not differ ($P = \text{NS}$) between treatments (23, 52 and 67 % frovatriptan vs. 30, 61 and 66 % comparators).

Conversely, the rate of recurrent episodes at 24 h was significantly ($P < 0.05$) lower under frovatriptan (11 vs. 24 % with comparators, Table 2). This was also the case for recurrence at 48 h (15 % frovatriptan vs. 26 % comparators, $P < 0.05$, Table 2). Differences in cumulative hazard of recurrences over the 48 h were in favor of frovatriptan (Fig. 1).

Safety results

A total of 18 drug-related adverse events were recorded in 401 treated menstrually related attacks. No statistically significant differences were observed in the rate of attacks associated with drug-related adverse events between frovatriptan (10/189 attacks, 5 %) and the comparators (8/194, 4 %).

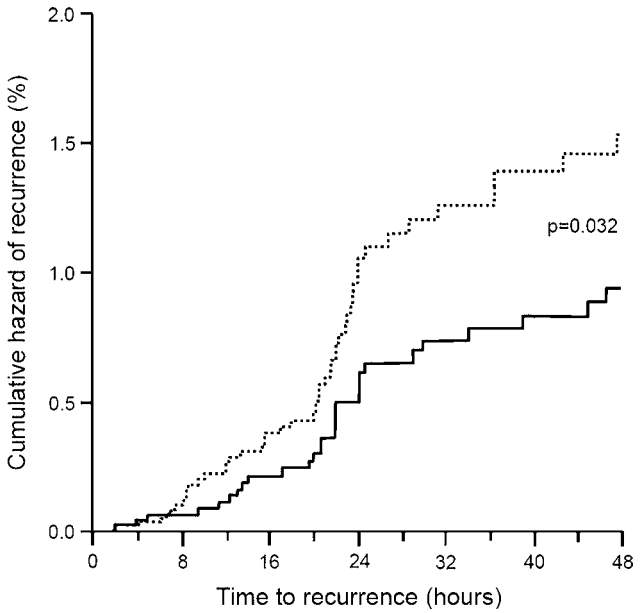

Fig. 1 Cumulative hazard of recurrence over 48 h during treatment with frovatriptan or comparators, in the 187 patients of the intention-to-treat (ITT) population. Data are shown separately for frovatriptan (*continuous line*) and for the three comparators pooled together (*dotted line*). P value refers to the statistical significance of the between-treatment difference

Discussion

In this pooled analysis of three double-blind, randomized, direct comparative, crossover studies [8–10], acute treatment of menstrually related migraine with frovatriptan and other triptans (rizatriptan, zolmitriptan and almotriptan), resulted in similar proportions of pain relief and pain free episodes at 2, 4 and 24 h. Despite a similar immediate antimigraine efficacy profile of the studied drugs, frovatriptan showed a more sustained relieving effect on migraine, with lower headache recurrence rates over 24 h and even more so over 48 h. Such differences might be

explained, at least in part, by differences in the pharmacokinetics of frovatriptan with respect to the other triptans. Frovatriptan has a longer elimination half-life than rizatriptan, zolmitriptan and almotriptan, this possibly explaining why frovatriptan, unlike the other tested triptans, greatly reduced the risk of recurrence [12].

This is the first analysis of head-to-head, double-blind, randomized trials of frovatriptan versus other triptans in women suffering from menstrual migraine. Our study and a retrospective analysis of almotriptan versus zolmitriptan are the only available double-blind, randomized studies comparing the efficacy of two triptans [13]. In a previous publication treatment of 136 women with almotriptan 12.5 mg and of 119 women with zolmitriptan 2.5 mg resulted in similar proportions of 2 h pain relief and pain free as well as 2–24 h recurrences between the two groups [13].

Though we acknowledge that the strength of our results might be weakened by the post hoc nature of the analysis, no such prospective studies are yet available or have been planned. Our results encourage the design and implementation of larger direct comparative randomized clinical trials evaluating triptan efficacy in female migraineurs.

In terms of safety, in our pooled analysis, treatment with frovatriptan and other triptans was associated with a similar low prevalence of adverse drug reactions. This reinforces evidence from prior placebo controlled or head-to-head trials, namely that frovatriptan, used for immediate or repeated sustained use, is one of the best tolerated among triptans [14–19].

In conclusion, our analysis of individual data of double-blind, randomized, crossover trials suggests that frovatriptan and other widely employed triptans share a similar efficacy in the immediate treatment of acute attack of menstrual migraine. However, frovatriptan seems to offer the advantage of a lower risk of recurrence and thus a more sustained effect than the other triptans.

Acknowledgments The present study was supported by Istituto Lusofarmaco d'Italia S.p.A.

Conflict of interest All authors have occasionally served as scientific consultants for the manufacturers of frovatriptan, rizatriptan, zolmitriptan or almotriptan. D. Zava is an employee of Istituto Lusofarmaco d'Italia.

Appendix

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Is migraine a risk factor for the occurrence of eating disorders? Prevalence and biochemical evidences

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Abstract The eating disorders (ED), anorexia nervosa (AN) and bulimia nervosa (BN), are severe psychiatric and somatic conditions occurring mainly in young woman. Although the aetiology is largely unknown, same evidences suggest that biological and psychological factors play a relevant role in the pathogenesis, along with monoamine, indole and same hypothalamic hormonal dysfunctions. Migraine is characterized by similar metabolic and psychological anomalies suggesting that a possible relationship exists between the two pathological conditions. To understand the possible relationship between migraine and ED, we have investigated the prevalence of migraine and the other primary headaches in a large group of AN and BN patients. In addition, we have studied the role of tyrosine metabolism in the same group of AN and BN young woman sufferers. In particular, we measured plasma levels of elusive amines: tyramine (Tyr) and octopamine (Oct) and catecholamines: noradrenalin (NE), dopamine (DA). The results of this study show that the prevalence of migraine in the woman affected by ED is very high (<75 %). The levels of Tyr and DA were higher and levels of NE were lower in the ED patients in respect to the control subjects. These biochemical findings suggest that abnormalities of limbic and hypothalamic circuitries play a role in the pathogenesis of ED. The very high prevalence of migraine in our group of ED sufferers and the biochemical profile of migraine, similar to that of ED patients shown in this study, suggest that migraine may constitute a risk factor for the occurrence of ED in young females. This hypothesis is supported by the onset of migraine attacks that initiated, in the majority of the patients, before the occurrence of ED symptoms.

Keywords Eating disorders · Migraine · Noradrenalin · Dopamine · Trace amines

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Introduction

Eating disorders (ED) such as anorexia nervosa (AN) and bulimia nervosa (BN) are severe psychiatric and somatic pathological conditions that occur mainly in young woman [1]. The aetiology of ED is poorly understood, although psychological and biological factors may play a significant role in the physiopathology of this disorder [2]. Among psychological factors depression, low self-esteem, insecure attachment, obsessive trait, anxiety, etc. seem to be identified, thus far, with a reasonable degree of evidence. Longitudinal studies have found that the same symptoms linked to these risk factors clearly precede the onset of the illness. Among biological factors, abnormalities of serotonin (5-HT), noradrenalin (NE) and dopamine metabolism have been reported in anorexic animal models and same human studies [3, 4]. The anomalous eating behaviour, the absence of menses and the low sexual appetite that characterize the ED disease suggests that anomalies in these neurotransmitters are localized in the limbic, hypothalamic and dopaminergic circuitries [5].

Intriguingly migraine presents similar catecholamine dysfunctions as ED [6]. In addition, the high levels of trace amines such as tyramine (Tyr) and octopamine (Oct), in plasma and platelets, recently found in migraine patients, suggest that anomalies of hypothalamic and limbic areas

contribute to migraine physiopathology, as trace amine-associated receptors are localized in the brain areas [7]. Indeed, many of the symptoms of ED patients are attributed to anomalies of the same brain regions [8]. However, whilst these findings suggest that migraine and ED may, to same degree, share similar underlying physiopathological aspects, no information is available to possible prevalence of migraine among ED patients and it is unknown whether anomalies in the metabolism of trace amines play a role in the pathogenesis of ED. To ascertain this hypothesis we, here, evaluated plasma levels of NE, dopamine (DA), Tyr and Oct in a large group of ED sufferers. We also assess the prevalence of migraine and the other primary headaches in the same patient sample.

Methods

NE, DA Tyr and Oct were measured in plasma of 109 patients affected by anorexia ($n = 89$, 71.2 %) or bulimia nervosa ($n = 36$, 28.8 %) and 27 healthy control subjects matched for age and sex with the patients. The diagnosis of each type of ED syndrome was, in accordance with the DSM-IV criteria [9], made utilizing the body mass index (below 17.5 for anorexia, under 17.5 for bulimia).

Forty-eight patients were free from pharmacological treatment (44 %); 61 (56 %) patients were under antidepressant therapies (Table 1). In the subject, peripheral venous blood (25 ml) was drown by the same operator from the antecubital vein, following overnight fasting, at 9 a.m. at supine position and collected in fr/10 volume citric acid/citrate dextrose as anticoagulant for estimation of the biochemical markers. Platelet poor plasma (PPP) was obtained as described elsewhere [10]. An aliquot of perchloric acid was added to PPP (total volume 4 mL) for the deproteinization. After brief centrifugation (14 000 rpm for 5 min.), the supernatant was passed through an ultrafilter membrane. The levels of NE, DA, Tyr and Oct were evaluated using an HPLC coulometric method.

Statistical analysis was conducted by SPSS version 13. Sample distribution were evaluated by Kolmogorov–Smirnov test. Groups with Gaussian distribution were compared by Welch t test, whilst groups displaying non-parametric distribution were compared by Mann–Whitney test.

A neurologist expert in the diagnosis and treatment of primary headaches interviewed all ED patients. Migraine and the other primary headaches present among ED sufferers were diagnosed in agreement of HIS diagnostic criteria [11].

Results

Biochemical results

NE was detected in plasma of 103 out of 125 patients and in all controls subjects, DA in 74/107 patients and 13/26 controls, Tyr in 106/107 patients and 25/27 controls, and Oct in 62/107 patients and 19/26 controls. In comparison to

Table 1 Characteristics of the population studied

	ED $n = 109$	AN $n = 76$ (69.7 %)	BN $n = 33$ (30.0 %)	C $n = 27$
Gender	All females			All females
Age (years)				
Mean ± SD	26.56 ± 8.498	26.18 ± 8.128	26.06 ± 8.778	27.73 ± 6.247
Range	16–58	16–58	17–56	20–53
BMI ± SD	17.29 ± 4.816	14.93 ± 2.488	22.53 ± 4.130	
Patient treated	61 (55.96 %)	42 (54.7 %)	19 (58.1 %)	
Antidepressive[a]	54	38	16	
Antipsychotic[b]	16	9	7	
Benzodiazepine[c]	37	26	11	
Patient without pharmaceutical therapy	48 (44.04 %)	34 (45.3 %)	14 (41.9 %)	27

ED eating disorders patient

AN anorexia nervosa

BN bulimia nervosa

C control subjects

[a] and stabilizzant (SSRI 20 mg/d, valproic acyd 400–600 mg/d)

[b] (densapro 5–10 mg/d)

[c] (bromazepan 3–6 mg/d)

the control subjects, the plasma levels of DA and Tyr were significantly higher in ED patients ($p = 0.05$, $p < 0.001$), whereas the plasma levels of NE were lower in the patient group ($p < 0.04$). The levels of Oct were in the same range in both subject groups (Table 2).

Upon comparison of the NE, DA, Tyr and Oct levels in the anorexic to those of bulimic patients and of the each group of those of the control subjects, we found that DA and NE plasma levels were in the same range in the two patient groups. In contrast, Tyr plasma levels were significantly higher in bulimic patient group when compared to levels found in both the anorexic and control groups ($p = 0.02$, $p = 0.03$, respectively). The Oct plasma levels were more elevated in anorexic group that those of the bulimic group ($p = 0.03$) and the Oct levels of the bulimic group were significantly lower than that of control subjects ($p = 0.05$) (Table 3).

Prevalence of primary headaches among ED patients

One hundred and nine patients affected by either anorexia ($n = 76$, 70 %) and/or bulimia nervosa ($n = 33$, 30 %), afferent to Center of Eating Disorders, were enrolled in the study. All subjects were female, age of them ranged 18–32 years (mean age range = 25). The diagnosis of migraine with and without aura of migraine or other primary headaches was made in accordance with HIS criteria [11] utilizing a questionnaire that included questions about the presence of migraine in parental first degree relatives of the patients and characteristics of the headache attacks, i.e. frequency and duration. Ninety-one ED patients complained primary headaches (84.4 %). Eighty-one ED patients satisfied HIS criteria for the diagnosis of migraine (89 %), of which 16 (55 %) present migraine without aura (MwwA), 3 (2.8 %) present migraine with aura (MwA), 5 (4.6 %) with probable MwwA, 8 (7.3 %) with possible MwwA and 5 (4.6 %) present a chronic migraine. Six (6.6 %) ED patients were affected by tension type headache, four (4.4 %) patients present non-classifiable headache. Twelve ED patients not suffering from migraine (11 %), but have a first degree relative affected by MwwA. In 68.1 % of patients the migraine attacks began prior to the onset of ED symptoms; in 15 patients, (16.5 %) the attacks initiated at the same time, and in the minority (14 patients, 15 %) migraine appeared after the onset of ED symptoms (Table 4). The frequency of the attacks in ED patients affected by migraine ranged 1–15 attacks/month and the duration between 8 and 72 h or more. No statistical differences in the frequency and duration of migraine attacks were found between the anorexic and bulimic patients.

Discussion

The results of this study indicate that a possible relationship exists between ED and migraine. The prevalence of migraine in woman affected by ED, at least in our patient series, is 74.5 % in comparison to that of the general population (12–15 %) [12] and, in the majority of patients, the onset of migraine attacks began before or in the same time of the onset of ED symptomatology [13]. The results of this biochemical study support this hypothesis. In comparison to control subjects, ED patients present significantly higher dopamine plasma levels, whereas noradrenalin, derived from its precursor dopamine, via the activation of dopamine β-hydroxylase enzyme activity [13], significantly lower plasma levels. The plasma levels of tyramine, product of tyrosine decarboxylase enzyme activity with tyrosine being the substrate [14], are significantly higher in ED than controls, whereas those of the octopamine are apparently similar in both patient groups.

Table 2 Plasma levels of tyramine, octopamine, noradrenalin, dopamine, in ED patients and control subjects

	ED ($n = 109$) M/SD	C ($n = 27$) M/SD	*p*
Tyramine	0.855/0.615	0.686/0.342	0.05**
Octopamine	1.178/1.736	1.293/1.354	NS*
Noradrenaline	104.264/115.509	153.181/73.197	0.039**
Dopamine	14.0037/17.018	2.877/4.119	0.001*

Values are expressed as ng/mL

M mean

SD standard deviation

ED eating disorders patient

C control subjects

* Mann-Witney 2-tailed unpaired test

Table 3 Plasma levels of tyramine, octopamine, noradrenalin, dopamine in anorexia, bulimic patient and control subjects

	AN M/SD	BN M/SD	C M/SD	*p*
Tyramine	0.774/0.565	1.087/0.699	0.686/0.342	AN versus C: NS**
				BN versus C: 0.035*
				AN versus BN: 0.026*
Octopamine	1.345/1.904	0.7082/1.022	1.293/1.354	AN versus C: NS**
				BN versus C: 0.05**
				AN versus BN: 0.03**
Noradrenalin	105.412/122.756	101.189/95.345	153.181/73.197	AN versus C: <0.001*
				BN versus C: 0.028**
				AN versus BN: NS*
Dopamine	12.849/16.537	17.261/2.877	2.877/4.119	AN versus C: 0.006*
				BN versus C: <0.001*
				AN vs. BN: NS*

Values are expressed as ng/mL

M mean

SD standard deviation

AN anorexia ner vosa

BN bulimia nervosa

C control subjects

* Mann–Witney 2-tailed unpaired test

** *t* test

Table 4 Prevalence of headache patients among ED sufferers

Total patient				
109				
Patient with headache				
91 (84.4 %)				
Migraine				
81 (74.3 %)				
MwA	MwwA	MwwAps	MwwApr	CM
3 (2.8 %)	60 (55 %)	8 (7.3 %)	5 (4.6 %)	5 (4.6 %)
Tension headache				
6 (5.5 %)				
ETH	CTH			
3 (2.8 %)	3 (2.8 %)			
Other headaches				
4 (3.7 %)				
Onset of headache	ED	AN	BN	
Before ED	62 (68.1 %)	46 (73.0 %)	16 (48.5 %)	
Corresponding to ED	15 (16.5 %)	10 (15.9 %)	5 (15.1 %)	
After ED	14 (15.4 %)	7 (11.1 %)	7 (25.0 %)	
Total patient	91	76	33	

MwA migraine with aura

MwwA migraine without aura

MwwAps migraine without aura possible

MwwApr migraine without aura probably

CM chronic migraine

ETH episodic tension headache

CTH chronic tension headache

However, when these data, which include both the anorexic and bulimic patent groups, are disaggregated, their profiles change. The anorexic patients show tyramine and octopamine plasma levels in the same range as those of controls. The only relevant data in this patient group are that the plasma levels of octopamine inversely correlate with BMI (Pearson test, $p < 0.04$) suggesting that the higher levels of octopamine are related with the severity of the anorexia. In contrast, in comparison to controls and anorexic subjects, tyramine is significantly higher and octopamine is significantly lower in the bulimics. The interpretation of this anomaly of tyrosine levels in ED patients is uncertain; however, the large accumulation in plasma of dopamine and the low levels of noradrenalin strongly suggest that the activity of DBH is reduced in both anorexic and bulimic patients. The different profiles of tyramine and octopamine plasma levels may indicate that the possible shift from anorexia to bulimic state may be related with differences in the metabolism of trace amines. It is, in fact, known that octopamine regulates the body mass through glucose and lipid metabolisms [15, 16]. The low levels of octopamine in the bulimic group may favour a glucose and lipid synthesis with an increase of body mass in these patients.

The pathophysiology of anorexia and bulimia is not completely understood; however, the obsessive control of the feeding behaviour, the change in body weight, reduced

sexual appetite and disappearance of menstrual cycle suggest that dysfunction of the hypothalamus [8], limbic centres [17] and amygdala [18] may play an important role in the pathogenesis. BOLD NMR studies show that these CNS structures are activated in ED patients when adequately stimulated with different kind of foods [19]. Moreover, the recovery from the ED symptoms seems to be accompanied by the activation of the lateral and apical prefrontal cortex, part of the limbic structure [17]. The increase of dopamine and tyramine along with a decrease of octopamine in bulimic patients support this hypothesis, since dopamine and elusive amine synthesis and their receptors (DA and TAARs) are localized in the limbic, amygdala and hypothalamic circuitries [20]. The activation of dopaminergic pathways, that is also reported in obsessive–compulsive syndromes, may play an important role in the fixation of the repetitive behaviour repertoires that characterize ED patients [21] and in the abnormal feeling of satiety in the anorexic sufferers [3].

Migraine seems characterized by similar biochemical findings. Migraine patients show, in comparison to control subjects, higher dopamine and lower noradrenaline levels in plasma and platelets [22]. In these patients, anomalous activity of DBH has been demonstrated, along with a polymorphism in the gene that controls the function of this enzyme [23]. In addition metabolism of elusive amines is also deranged in migraine patients [24]. This, together with the premonitory symptoms that precede the migraine attacks (nausea, depression, thirst, sexual excitement, anger, hyperosmia, etc.) suggest that a hypothalamic and limbic disfunction(s) play a role in pathogenesis of migraine [25–27].

In conclusion, the data, here shown, indicate that ED is characterized by an anomalous tyrosine metabolism, with a very high circulating levels of dopamine and tyramine and low levels of noradrenalin and octopamine (the latter amine at least in bulimic group). These findings support the hypothesis that metabolic derangement in the limbic, amygdala and hypothalamus centres play a role in the aetiology of ED. This biochemical profile is similar to that of migraine and the prevalence of migraine is overwhelming among ED sufferers. All these evidences suggest that migraine may constitute a risk factor for the occurrence of ED.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

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Food as trigger and aggravating factor of migraine

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Abstract A relevant proportion of patients say that their migraine attacks may be precipitated by dietary items, the percentage of patients reporting foods as trigger ranging in different study from 12 to 60 %. Fasting, alcohol, chocolate and cheese are the dietary precipitating factors more frequently reported. The finding that diet-sensitive migraineurs are usually sensitive to several and different foods, lead to the hypothesis of antigenic similarities between these disparate foods or common chemical constituents, but a clear scientific explanation of the mechanisms implicated in the development of migraine attacks supposedly precipitated by food is still lacking. The possibility that the elimination diets based on the hypothesis of food hypersensivity IgE or IgG-mediated improve migraine has been explored in different studies but the results are inconclusive. Fasting as trigger for migraine is frequently reported. Some migraineurs show reactive hypoglycaemia due to diet-induced hyperinsulinism. In conclusion, identification of environmental factors (including dietary factors) that consistently trigger migraine in some subjects may be helpful to reduce attacks frequency. The biological mechanism by means of triggers in general and food in particular precipitate migraine attacks remains obscure.

Keywords Migraine · Triggers · Food · Elimination diet · Reactive hypoglycaemia

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Introduction

The exact pathophysiology of migraine is still unclear but clinical experience and many electrophysiological studies [1] demonstrated an increased sensitivity of the brain of the migraineur. It is therefore not surprising that in this sensitised brain migraine may be triggered by external and internal stimuli. A number of precipitating factors have been identified in the literature [2–7]. Kelman [7] retrospectively evaluated 1,207 patients affected by migraine: 75.9 % reported triggers (40.4 % infrequently, 26.7 % frequently and 8.8 % very frequently). The triggers were in order of frequency: stress (79.7 %), hormones in women (65.1 %), not eating (57.3 %), weather (53.2 %), sleep disturbance (49.8 %), perfume or odour (43.7 %), neck pain (38.4 %), light(s) (38.1 %), alcohol (37.8 %), smoke (35.7 %), sleeping late (32.0 %), heat (30.3 %), food (26.9 %), exercise (22.1 %) and sexual activity (5.2 %).

The relationship between diet and migraine is complex and includes many aspects such as identification of specific foods as trigger factors, the role of food hypersensivity and elimination diets, the mechanisms implicated in the development of migraine attacks supposedly precipitated by food and the role of fasting and glucose metabolism.

Food as trigger factor

More than 50 years ago, Selby and Lance [8] noticed that a relevant proportion of patients report that their migraine attacks are usually precipitated by dietary items. The percentage of patients reporting foods as trigger for migraine range in different study from 12 to 60 % with many subjects reporting more than one [7, 9–12]. Peatfield et al. [13] found that 19.2 % of migraine patients reported sensitivity to

cheese, 18.2 % to chocolate and 11.1 % to citrus fruit. In Timi Fukui series [10], alcohol (34 %) and chocolate (20.5 %) were the most frequently implicated factors and wine (in particular red wine) was significantly more common as a trigger in women than men. In the same paper, coffee is reported to precipitate migraine by 14 % of patients, while other foods (sausage, salami, monosodium glutamate, cheese, milk, aspartame, soft drink, citric fruits, ice-cream and nuts) play a role in less than 10 % of subjects. Hauge [11] studied a group of patients with migraine with aura. The comparison of individual trigger factors in attacks of migraine with aura (MA) and migraine without aura (MO) did not show differences in term of attacks precipitated by food and seasoning while MO attacks were more frequently induced by wine, beer or other alcoholic beverages. Kelman [7] found that patients with MA had in general more precipitating factors, including dietary ones, than patients with MO (stress, not eating, weather, sleep disturbance, sleeping late, perfume/odour, lights, alcohol, heat, food and exercise). In the same study, migraineurs with triggers (dietary ones or others) were found to have more family members with migraine, a longer lifelong duration of migraine, a more florid migraine profile (higher frequency and duration of attack) as well as more comorbidity and sleep difficulties than migraineurs without triggers.

We evaluated dietary triggers in 100 subjects affected by MO according the International Classification of Headache Disorders (ICHD)-2 diagnostic criteria [14], consecutively seen in the Headache Centre of University of Genova. Demographic and headache characteristics are shown in Table 1.

Migraine attacks were triggered by food at least occasionally in 20 patients. In all subjects the attacks precipitated by food appear within 24 h since ingestion. The foods more frequently involved were chocolate (45 %), cheese (30 %), wine (20 %), tomatoes (20 %), carbohydrates (20 %), leavened products (15 %) and nuts (10 %). Multiple dietary triggers were reported by 55 % of subjects.

Food hypersensivity and elimination diets in migraine

Since the 1930s, several studies evaluated elimination diets in migraine patients, with conflicting results [15–18]. An individualised approach of the diet to relieve migraine is desirable. Currently, the best accepted method for diagnosing and confirming food hypersensitivity is empirical, by elimination diet and challenge but this method is laborious, and it is difficult to test all the combinations of food types that may precipitate the attacks. Thereafter, many triggers are experienced occasionally and not consistently by the patients.

Table 1 Demographic and headache characteristics

	Total	Males	Females
Number	100	11	89
Age	41.7 ± 14.2	33.5 ± 9.9	42.7 ± 14.4
Duration of migraine (years)	19.3 ± 13.3	16.3 ± 7.4	19.6 ± 13.9
Monthly attacks frequency	6.8 ± 5	4.5 ± 2	7.1 ± 5.2

In the majority of studies showing significant improvement when patients were put on an elimination diet, the dietary restrictions were based on the identification of food allergies by different mechanisms.

Previous studies reported a success in reducing migraine attacks of individualised diet based on food intolerance tested by the presence of IgE antibodies, which are believed to determine the "immediate response" [19].

More recent studies tested diets based on the identification of food specific IgG antibodies which characteristically exhibit a slower response [20–22].

Arroyave Hernandez [20] investigated 56 patients with recurrent attacks of migraine (at least once a month) and 56 control subjects without migraine and measured their allergen-specific IgG against 108 food allergens by enzyme immunoassay. The authors reported that there was a statistically significant difference in the number of positive results for IgG food allergens between patients and controls and that the elimination diet improved the migraine without need of medication.

Alpay [21] conducted a double-blind, randomised, cross-over trial about diet restriction in migraine, based on IgG against foods. He found a statistically significant reduction in the number of headache days (from 10.5 ± 4.4 to 7.5 ± 3.7; $P < 0.001$) and number of migraine attacks (from 9.0 ± 4.4 to 6.2 ± 3.8; $P < 0.001$) in the elimination diet period.

Mitchel [22] did a randomised, controlled trial of food elimination diet based on IgG antibodies for the prevention of migraine-like headaches. Elimination diet did not reduce the disability or impact on daily life of migraine-like headaches, or the number of migraine-like headaches at 12 weeks, but it significantly reduced the number of migraine-like headaches at 4 weeks. This study shows a major limitation, because the diagnosis of migraine was not based on International Classification of Headache Disorders (ICHD)-2 diagnostic criteria [14], but was self-reported by patients.

In short, the results of the elimination diets based on the hypothesis of food hypersensivity IgE or IgG-mediated are inconclusive.

Mechanisms implicated in the development of migraine attacks precipitated by food

A clear scientific explanation of the mechanisms implicated in the development of migraine attacks supposedly

precipitated by food is still lacking. According to the hypothesis that see the migraine as an evolutionary conserved reaction consistent with sickness behaviour [23] engendered to restore a disturbed homeostasis of the brain, we can look at the different triggers as elements able to cause a dysfunction in the interoceptive system. The finding that diet-sensitive patients are usually sensitive to several and different foods, leads to the idea that they share a common pathogenic mechanism: antigenic similarities between these disparate foods or a common chemical constituent [24].

The first hypothesis advanced was the so-called 'amine hypothesis' but clinical challenge tests with substances like tyramine or b-phenylethylamine were inconsistent [25]. The next step was to investigate the amines' metabolic routes to verify if the elimination pathways of such amines is deficient in migraine patients who report dietary triggers. In humans, amines have two major elimination pathways such as oxidation by monoamine oxidase (MAO) to parahydroxyphenylacetic acid and sulphation by phenosulphotransferase to water-soluble conjugates.

Some studies found in migraineurs a low platelet MAO-B activity, but only during migraine attacks, without differences between patients who are sensitive to dietary triggers and patients who are not [25].

A reduced urinary output of sulphated tyramine metabolites after an oral tyramine load in subjects with food-sensitive migraine was reported, but the data about the activity of the two forms of phenosulphotransferase in migraine patients were inconclusive [26]. Finally, patients who had a food-sensitive migraine do not seem to have an increased amines' intestinal absorption [25].

A second hypothesis, supported, as we have seen, by the studies on elimination diets, explicates food-trigger migraine by means of an "allergic" mechanism [15–22]. The hypersensivity may be mediated by IgE antibodies, the interaction of a food constituent with a specific IgE antibody producing a response by the activation of complement or degranulation of mast cells. However, IgE levels or complement activation were not found elevated during migraine attacks [27].

Non-IgE antibody-mediated mechanisms have also been proposed in food allergy [28]. Food-allergy antigens, transported by way of mast cells, activate T helper and B lymphocytes and increase the production of IgG antibodies and cytokines, leading to an inflammation response, which is known to play an important role in the pathophysiology of migraine attacks.

Some foods might trigger migraine by a further mechanism, which involves histamine-induced vasodilatation, due to nitric oxide liberation from the endothelium [29].

Fasting, glucose metabolism and migraine

Between the dietary triggers of migraine attack, fasting is very frequently reported, with percentages which range from 39 to 66 % [2–14]. In clinical practice, patients frequently report that an appropriate "dosing" of carbohydrates (avoiding fasting and/or skipped meals) is useful to prevent the migraine attack. On the other hand, foods with a high glycemic index can result in a rapid increase in blood glucose followed by a rapid drop which is associated with the beginning of migraine attack.

Dexter [30] performed a standard oral glucose tolerance test (100 g glucose) on 74 migraineurs. Glucose tolerance curves were consistent with a classification of diabetes and reactive hypoglycaemia in 8 and 72 % of migraine patients, respectively. Subsequent dietary therapy with a low sucrose six-meal regimen resulted in at least 75 % reduction of attacks frequency in all diabetic patients (100 %), and most migraineurs (63 %) who previously demonstrated reactive hypoglycaemia. This reactive hypoglycaemia seems to be due to diet-induced hyperinsulinism [31].

Cavestro [32] compared glucose and insulin concentrations in 84 migraineurs, 25 headache patients, and 26 non-migraine/headache controls and confirmed that an elevation in glucose may be associated with headaches in general, but elevated insulin level seems to be specifically associated with migraine attacks.

In all migraineurs, a well-balanced diet and avoidance of fasting or skipped meals have to be encouraged. Low glycemic index snacks may be beneficial between meals and light snacks before bedtime may reduce the onset of early morning migraine.

Finally, it has been reported that diet with low-fat intake could reduce the headache frequency and intensity [33].

Conclusions

Identification of environmental factors (including dietary factors) that consistently trigger migraine in some subjects may be helpful to reduce attacks frequency. A key question remains unanswered. By what biological mechanism do triggers in general and food in particular precipitate migraine attacks? We can suppose that triggers are able to destabilize subcortical structures integral to homeostasis, activating genetically sensitised pathways involved in the migrainous head pain. Understanding how this can happen may address to a better comprehension of migraine pathophysiology.

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

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Migraine and metabolism

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Abstract Migraine is a chronic disorder with complex pathophysiology involving both neuronal and vascular mechanisms. Migraine is associated with an increased risk of vascular disorders, such as stroke and coronary heart disease. Obesity and diabetes are metabolic disorders with a complex association with migraine. Insulin resistance, which represents the main causal factor of diseases involved in metabolic syndrome, is more common in patients with migraine. A better understanding of the relationship between metabolic syndrome and migraine may be of great clinical interest for migraine management.

Keywords Migraine · Metabolic syndrome · Obesity · Vascular disease

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Introduction

Migraine is a chronic disorder with complex pathophysiology involving neuronal and vascular mechanisms. An association between migraine, especially with aura, and vascular disorders such as coronary heart disease and stroke has been reported in previous studies [1–3]. Obesity and diabetes are metabolic disorders which also have a complex association with migraine. Although some clinical and population-based studies demonstrated a lower migraine prevalence in patients with diabetes mellitus [4, 5], a similar [6] or higher prevalence [7, 8] was found in other studies. The underlying mechanism of these comorbidities is still unknown. Insulin resistance, which is accepted as a causal factor for the development of hypertension, diabetes mellitus, obesity, cardio- and cerebrovascular disorders, has recently been shown also to exist in nonobese migraine patients, although in a small case–control study [9–14]. Among latter ones, obesity was found to be a risk factor for chronic and transformed migraine, although migraine by itself was not more prevalent in obese patients [15]. Several studies were designed to assess the association between migraine and diabetes [16], and between migraine and vascular disorders [1, 17], but it was commonly disregarded if the patients had also metabolic syndrome. Some drugs used to treat metabolic disorders showed a significant efficacy in migraine prophylaxis [18–22]. In this review, we explored some of the possible clinical and experimental links between migraine and metabolic syndrome.

Metabolic syndrome

Metabolic syndrome (or insulin resistance syndrome) is directly related to obesity and other cardiovascular risk

factors. Components of the metabolic syndrome include insulin resistance, visceral adiposity, dyslipidemia, hypertension, and elevated levels of inflammatory markers, as well as prothrombotic and pro-inflammatory peptides [23]. As defined by Adult Treatment Panel III, metabolic syndrome requires at least three of the following five characteristics: trunk obesity (waist circumference), increased fasting glucose, hypertension, low high-density lipoprotein (HDL), and increased triglycerides [24]. A recent study observed that the 1-year migraine prevalence in metabolic syndrome is 11.9 % in men and 22.5 % in women, while several large population-based studies showed a 1-year prevalence of migraine in western countries of 5–5.7 % in men and of 12–17.7 % in women [25–27]. Metabolic syndrome has also been associated with chronic pain: a recent study observed that women with fibromyalgia were five times more likely to have metabolic syndrome than healthy controls [28].

Obesity

Migraine and obesity represent two major public health problems. Both disorders are prevalent particularly in the USA, where 12 % of individuals are migraineurs and one-third of the subjects are obese [29, 30]. Recent studies suggest that obesity and migraine may be directly linked [15, 31, 32]. Particularly, obesity is associated with higher prevalence of migraine, especially with aura, higher attack frequency, greater attack severity, and increased photophobia and phonophobia frequency [15, 33, 34]. Weight loss, which is an important factor for the reduction of the cardiovascular risk in metabolic syndrome, might also prevent migraine and decrease its frequency [25, 35]. According to ATP III criteria, waist circumference (WC) measurement is advised to detect any excess in weight. Guldiken et al. observed that patients with metabolic syndrome and migraine were more prone to have a WC above the cutoff values. Actually, WC is a marker of abdominal fat accumulation and indirectly indicates insulin resistance and elevation of proinflammatory cytokines levels. This supports the hypothesis that increases in body adipose tissue would raise the risk of migraine attacks [25]. Migraine and obesity may also be linked from a biochemical perspective [36, 37]. Both disorders are pro-inflammatory states. Migraine is defined as a "neurogenic inflammation": the source of pain in migraine headache may involve neurogenic plasma extravasation and consequent vascular meningeal inflammation [38]. Many inflammatory promoters are altered in migraineurs [39]. Trigeminal ganglion stimulation also causes release of a powerful vasodilator peptide, vasoactive intestinal polypeptide (VIP), through a reflex activation of the cranial parasympathetic outflow [40]. In obese subjects, adipocytes can secrete a variety of cytokines, including IL-6 and tumor necrosis factor, which are cytokines that promote inflammation [36, 37]. Obesity, like migraine, is associated with increased CGRP levels [41]. Peterlin et al. [42] showed that low levels of adiponectin are decreased in obesity and has an impact on the severity of migraine attacks. Adipose tissue, as an endocrine gland, produces several inflammatory cytokines, including interleukin-6 and tumor necrosis factor-α, and causes low-grade inflammation of the vascular system and a prothrombotic state [43].

Diabetes mellitus type 2

Insulin resistance is the core of diabetes mellitus type 2, which is the most important cardiovascular risk factor [44]. Guldiken et al. observed that more than 75 % of patients with metabolic syndrome had impaired glucose metabolism, when compared with 12.6 % of healthy subjects. This striking difference can be explained by the overestimation induced by the population-based design of the present study [25]. Additionally, diabetes mellitus was more frequent in patients with migraine when compared with those without migraine. Nevertheless, the relationship between diabetes and migraine is still unclear, and there are conflicting results about the migraine prevalence in diabetes [45]. Aamodt et al. found an inverse relationship between diabetes mellitus and migraine frequency, particularly in middle-aged and elderly persons whose diabetes duration is more than 13 years old. Therefore, it has been speculated that diabetes mellitus may represent a protective factor against migraine [46]. A diabetic polyneuropathy may reduce vascular reactivity and prevent the onset of a migraine attack [47]. Additionally, numerous neurotransmitters such as nitric oxide, noradrenalin, and substance P are reduced in nerve terminals in diabetic neuropathy and this may be relevant to migraine pathophysiology [48, 49]. Split et al. [50] demonstrated a higher frequency of migraine in 154 noninsulin-dependent diabetes mellitus patients than in control subjects [50]. Therefore, we suggest that subjects with migraine should be carefully evaluated for impaired glucose metabolism. The association between migraine and ischemic vascular events has been studied for many years [51, 52]. Migraine, specifically migraine with aura, is an established risk factor for subclinical ischemic lesions of the brain, as well as for ischemic stroke [53–56].

Vascular disorders

Recent evidences linked migraine to a broader range of ischemic vascular disorders, including coronary disease [57–59]. Studies of subclinical markers of vascular disease

show that migraine is associated with retinopathy and with small vessel arteriolar intimae thickening, suggesting that migraine is related to atherosclerosis overall [50]. Hypertension may be of importance for migraine progression. Migraine patients were more likely to have increased blood pressure (BP; systolic BP >140 mmHg or diastolic BP >90 mmHg [OR = 1.76; 1.04–3.0]) and increased Framingham scores when compared with controls. In the Frequent Headache Epidemiology Study, both hypertension and diabetes were associated with chronic daily headache [1]. In the Genetic Epidemiology of Migraine study, migraineurs were more likely to report a parental history of early myocardial infarction. Migraineurs with aura were more likely to have an unfavorable cholesterol profile, increased BP (systolic BP >140 mmHg or diastolic BP >90 mmHg), and history of early-onset coronary disease or stroke. The risk of having an increased Framingham Risk Score for cardiovascular disease was approximately doubled for the migraineurs with aura. Overall, dyslipidemia is also more frequently associated with migraine [1]. HDL cholesterol has anti-inflammatory properties that may diminish neurodegenerative processes and the perception of pain [60]. Migraine is also considered to be a prothrombotic state by itself. Migraine with aura is a risk factor for stroke, angina, sudden death, and elevated cardiovascular risk factors. Additionally, migraineurs are more likely to have mutation of the Arg506Gln gene related to factor V, as well as protein S deficiency [61]. In young patients with ischemic stroke, migraine may be associated with a higher frequency of hypercoagulable states [62]. Randomized, double blind, placebo-controlled crossover studies, with lisinopril, an angiotensin converting enzyme inhibitor, and candesartan, an angiotensin receptor blocker, showed significant efficacy in migraine prevention [18, 19]. Simvastatin, a lipid-lowering agent, largely used to reduce the risk of initial and recurrent adverse ischemic cardiovascular and cerebrovascular events, has been reported to be effective in migraine prevention. The pleiotropic effects of statins, including anti-inflammatory properties and regulation of endothelial cell function and vasomotor reactivity, provide a plausible mechanism for a potential therapeutic effect in migraine [20]. Acetylsalicylic acid (ASA) seems to act peripherally upon cyclooxygenase at the vessel site, blocking painful inflammatory processes caused by the release of vasoactive neuropeptides from free C-fiber endings [21]. Various clinical studies suggest the efficacy of ASA in migraine prophylaxis [22]. Ginkgolide B may be considered a promising pharmacological aid for the treatment of migraine with aura due to its antagonizing effect on platelet activating factor (PAF). It is a potent proinflammatory and nociceptive agent released during the inflammation processes [63, 64]. Recently, it has been observed that omega 3 therapy may be effective in migraine prophylaxis [65].

Conclusion

The metabolic syndrome disorder components, such as increased waist circumference, obesity, and impaired glucose metabolism, were more frequent in migraine. It is suggested that insulin resistance might underlie a common pathogenesis of both disease, and this might be responsible for the higher migraine prevalence in metabolic syndrome. A better understanding of the determinants of the relationship between metabolic syndrome and migraine is of great clinical importance and a crucial step toward public health initiatives which aim to prevent migraine progression.

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Headache, eating and sleeping behaviors and lifestyle factors in preadolescents and adolescents: preliminary results from an Italian population study

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Abstract Several dietary and lifestyle habits can be associated with headaches or with their progression to chronic forms in adults. We report the results of the first population study performed in Italy on a sample of preadolescent and adolescent students to assess the possible association between headache and specific habits and lifestyle factors. Preliminary data from 800 questionnaires showed that 365 subjects had headaches, which were of moderate–severe intensity, associated with anorexia, and caused absence from school in more than 50 % of students. The main finding was the evidence of a clear association between headache and irregular intake of meals (especially irregular breakfast) and sleep disturbance with significant differences when subjects with and without headache were compared. If confirmed, these results are likely to influence clinical practice as well to address educational programs in preadolescents and adolescents.

Keywords Headache · Lifestyle · Eating behaviors · Sleep disturbances · Preadolescent · Adolescent · Epidemiology

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Introduction

Headache is one of the most frequently reported health complaints among adolescents. Epidemiological studies showed that 58.4 % of children and adolescents report headaches, with higher prevalence in females [1–5]. Migraine occurs in 5–11 % of the adolescent population and tension-type headache (TTH) in 5.1–18 % [1–4], while the prevalence of chronic daily headaches is estimated to be around 3 % [5].

Several studies investigated the potentially modifiable factors associated with headache and with its progression to chronic forms [6]. Dietary habits and some lifestyle factors were found to be associated with headaches in adults [7–9]. Anecdotal evidence suggests that a healthy lifestyle including regular physical exercise, a healthy diet, and weight loss may improve headache in children and adolescents. However, a few population-based studies investigated this issue [10–14].

We conducted a population survey to evaluate the possible relationships between headache, eating and sleeping behaviors and other lifestyle factors in preadolescents and adolescents.

Materials and methods

Data collection

Five schools have been asked to submit a structured self-administered questionnaire to their students. Students had to be 10 years or older and capable to self-complete the questionnaire.

Questionnaire

The questionnaire used for this survey covered five different areas :(1)"Demographic characteristics": sex, age, school level, height and weight; (2) "Clinical history of headache", including information about having or not having headache, the number of days with headache per month, the duration of headaches, the effects and the limitations of headache on daily life, previous medical consultations (GPs or specialists), the use of drugs to relieve pain, absence from school caused by headache; (3) "Sleeping habits", namely, the number of hours of sleep, the frequency of disturbed sleep and usual bedtime; (4) "Eating behaviors", such as following a diet, regularity of meals during the week, frequency of between-meal consumption of foods and beverages, fruit and vegetable consumption; (5) "Lifestyle attitudes" as coffee and illegal drugs consumption, smoking, and physical activity.

All the questions required multiple choice answers, and most had graded responses (e.g. "Never", "Sometimes", "Always" or "Never", "Few days a week", "Every day of the week").

Statistical analysis

Descriptive statistics were performed on all the categorical and continuous outcomes as count and percentages and mean and standard deviation, respectively. Subjects with and without headache were compared with the Chi-square test or the Fisher exact test, as appropriate. The multivariate logistic regression was used to compare headache and non-headache subjects considering all the independent factors with a backward approach. All the tests were two-tailed significance set to $\alpha = 0.05$ and with 95 % confidence interval.

Results

Eight hundred and two questionnaires were preliminary analyzed as November 2011. The study is still ongoing and we expect that the number of the completed questionnaires will exceed two thousands. Only two questionnaires were

Table 1 Main demographic and clinical characteristics of the study sample

	n (%)
N	800 (100)
Sex	
Females	321 (40.6)
Males	471 (59.4)
ns	9
Age (years)	
10–13	132 (16.6)
14–17	292 (36.7)
18+	372 (46.7)
ns	4
School level	
Elementary school	26 (3.3)
Secondary school	123 (15.4)
High school	651 (81.4)
Headache	
ns	3
No	432 (54.2)
Yes	365 (45.8)
Only for the 365 subjects who claimed to suffer from headache	
Headache frequency (no. of days per month)	
<1	94 (28.5)
1–4	97 (29.4)
5–9	68 (20.6)
10–19	55 (16.7)
20+	16 (4.9)
ns	35
Pain intensity	
Severe	40 (11.6)
Moderate	164 (47.4)
Mild	142 (41.0)
ns	19
Headache duration	
The whole day	70 (20.2)
Few hours	256 (74.0)
Few minutes	37 (10.7)
During the weekend	25 (7.2)
During menstruations[a]	67 (42.4)
ns	19
Associated symptoms	
Vomit	19 (5.6)
Cannot eat	63 (18.6)
Can eat normally	202 (59.8)
Photophobia	176 (52.1)
ns	27

ns not specified

[a] Referred only to females

Table 2 Univariate and multivariate analysis

	Headache (yes) 365 *n* %	Headache (no) 432 *n* %	*P* value
Sex			
Females	165 (45.7)	154 (36.1)	0.006
Males	196 (54.3)	273 (63.9)	
ns	4	5	
Age (years)			
10–13	59 (16.3)	73 (16.9)	0.754
14–17	137 (37.9)	152 (35.3)	
18+	166 (45.9)	206 (47.8)	
ns	3	1	
Diet			
No	319 (89.6)	383 (89.3)	0.881
Yes	37 (10.4)	46 (10.7)	
ns	9	3	
BMI (body mass index)			
<18.5 (underweight)	58 (17.3)	75 (19.0)	0.760
18.5–24.9 (normal weight)	247 (73.5)	280 (71.1)	
>25 (overweight)	31 (9.2)	39 (9.9)	
ns	29	38	
Breakfast			
Never	95 (26.3)	58 (13.9)	<0.0001
Sometimes	89 (24.7)	81 (19.4)	
Everyday	177 (49.0)	279 (66.8)	
ns	4	14	
Meals			
Irregular intake	196 (54.8)	155 (37.1)	<0.0001
Regular intake (3 meals every day)	162 (45.3)	263 (62.9)	
ns	7	17	
Extra meals			
Less than one a day/never	79 (22.1)	110 (25.8)	0.346
One a day	128 (35.9)	157 (36.8)	
Twice or more a day	150 (42.0)	160 (37.5)	
ns	8	5	
Sleeping badly			
Sometimes/always	275 (79.5)	276 (68.8)	0.001
Never	71 (20.5)	125 (31.2)	
ns	19	31	
Sport activities			
No	84 (23.3)	98 (22.8)	0.871
Yes	276 (76.7)	331 (77.2)	
ns	5	3	
Coffee			
Never/almost never	170 (48.2)	206 (48.4)	
Some days/everyday	183 (51.8)	220 (51.6)	0.956
ns	12	6	
Smoking			
Never/almost never	239 (66.9)	283 (65.6)	0.916
Some days/everyday	118 (33.1)	142 (33.4)	
ns	8	7	
Drugs			
Never	288 (82.5)	343 (81.5)	0.929
Almost never	27 (7.7)	35 (8.3)	
Some days/everyday	34 (9.7)	43 (10.2)	
ns	16	11	
Multivariate analysis (independent predictors of cephalalgy)[a]	OR (95 % CI)	*P* value	
Sex			
Males	1 (ref.)	0.0150	
Females	1.5 (1.1–2.1)		
Meals			
Irregular	1 (ref.)	0.0004	
Regular	1.8 (1.3–2.5)		
Sleeping badly			
Never	1 (ref.)	0.0194	
Always	2.6 (1.1–6.2)		

All the listed variables were placed in the model

ns not specified, % column percentage, *OR* odds ratio, *95 % CI* 95 % confidence interval

[a] The model retained the only significant predictors ($\alpha < 0.05$) with the backward approach technique

excluded because of non-plausible answers. The demographic characteristics of the sample and details about the frequency, severity and other main issues pertaining headache are summarized in Table 1.

Three hundred and sixty-five students declared to suffer from headache. Headache attacks lasted "at least few hours" in 74.0 % and "1 day" in 20.2 % of students. "Moderate" and "severe" intensity was reported by 47.4 and 11.1 %, respectively. The percentages of students who reported photophobia, anorexia and vomiting during attacks were 52.1, 18.6, and 5.6 %, respectively. Most of them (64.0 %) had to take a drug to relieve pain. Headache caused absence from school "sometimes" and "always" in 48.4 % and 2.3 %, respectively. Only 21.6 % declared frequent headaches (>10 days per month), and 4.9 % reported very frequent headaches (>20 days per month).

Students with and without headaches were compared as far as the variables concerning the five areas of

the questionnaire. Results are reported in Table 2. Those who suffered from headaches were prevalently women ($P = 0.006$), irregular meal consumers ($v < 0.0001$), particularly during breakfasts ($P < 0.0001$), and reported more sleeping problems ($P < 0.0001$).

Independent predictors of headache were female sex (OR, 95 % CI 1.5, 1.1–2-5), irregularity in meals (OR, 95 % CI 1.8, 1.3–2.5), and having sleeping problems (OR, 95 % CI 2.6, 1.1–6.2). Individuals belonging to the "worst forms" (who reported more frequent or more painful attacks) were also those who skipped more often meals and had more disturbed sleep. The use of coffee and drugs, smoking, physical activities as well "body-mass-index" (BMI) values were not associated with headache.

Discussion

We report the results of the first population study performed in Italy on preadolescents/adolescents to assess possible association of headache with specific habits and lifestyle factors.

The main finding is a clear association between headache and irregular intake of meals (especially irregular breakfast) and sleep disturbances. In contrast, lifestyle habits, such as regular smoking and consumption of caffeine or illicit drugs, physical inactivity and being overweight were not associated with headache in our study.

Studies in adults [7–9] found association between headache and skipping meals as well as high consumption of caffeine or alcohol, regular smoking or physical inactivity. Only a few studies are available on these issues [10–14]. A limited number of risk factors were evaluated in adolescents: smoking [11, 13, 14], physical inactivity [10, 11, 13], consumption of alcohol [10, 11] or coffee [10, 11]. In a recent study [10], in which a wide range of factors were evaluated, smoking, physical inactivity, and high consumption of cocktails and coffee were significantly associated with headache (migraine and TTH), while no correlation was found with skipping of meals.

Our study has some limitations: the major being the relatively small sample, and the fact that we evaluated headache, in general, without distinguishing the different clinical forms.

Concluding remarks

Our results suggest that preadolescents and adolescents with headache may have different habits in comparison with non-headache students, which may contribute to the development/worsening of headaches. If they will be confirmed in a large sample, they may have important implications, mainly because the correction of eating and sleeping behaviors could support the management of young patients with headache in clinical practice through educational programs aimed to headache prevention.

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Functional neuroimaging in migraine: usefulness for the clinical neurologist

Gioacchino Tedeschi · Antonio Russo · Alessandro Tessitore

Abstract Migraine is a common, multifactorial disorder, typically characterized by recurrent attacks of throbbing unilateral headache, autonomic nervous system dysfunction and, in approximately one-third of cases, neurological transient symptoms (migraineous aura). The diagnosis of primary headaches is exclusively a clinical task but, for this reason, it is sometimes subjective and arbitrary. However, until today no single diagnostic tool is able to define, ensure or differentiate idiopathic headache syndromes, although, in the clinical setting, conventional neuroimaging techniques are often widely and improperly used in headache patients. Recent years have seen rapid growth of neuroimaging methodology which has provided new insights into functional brain organization of migraine patients. Although functional magnetic resonance imaging has today little or no value in clinical practice, clinicians role is crucial since without a proper clinical selection neuroimaging studies could generate inconclusive results. Likewise, functional neuroimaging is crucial for clinicians in order to further elucidate pathophysiological mechanisms underlying this complex and often disabling disease and to provide new therapeutical approaches for migraine patients.

Keywords Migraine · fMRI · BOLD · Neuroimaging · Neurologist · Clinical practice

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Introduction

Migraine is a common, multifactorial disorder, typically characterized by recurrent attacks of throbbing unilateral headache, autonomic nervous system dysfunction and, in approximately one-third of cases, neurological transient symptoms (migraineous aura) [1]. Migraine is one of the most prevalent neurological diseases in adults, with a lifetime prevalence of up to 33 % in females and 13 % in males and frequently may become a very disabling disorder [2, 3]. Indeed, according to the World Health Organization migraine is ranked number 12 amongst women and 19 in the general population for the degree of handicap it causes [4].

The diagnosis of primary headaches is exclusively a clinical task [2] but, for this reason, it is sometimes subjective and arbitrary. However, until today no single diagnostic tool is able to define, ensure or differentiate idiopathic headache syndromes, although, in the clinical setting, conventional neuroimaging techniques are often widely and improperly used in headache patients. In fact, the routine use of conventional neuroimaging in migraine patients may be warranted only if atypical headache patterns, history of seizures and/or focal neurological signs or symptoms are present [5]. Despite these evidences, in many cases evaluation with computed tomography (CT) and magnetic resonance imaging (MRI) is performed, to rule out an underlying severe neurological disorder [6].

In the last decades, the study of the pathophysiology of primary headaches has been revolutionized by functional neuroimaging in vivo, which greatly improved the knowledge of physiological or dysfunctional neuronal activity in migraine. Indeed, animal or laboratory models mimicking the complexity of primary headache cannot be used in basic science research [7] whereas functional

neuroimaging in humans have allowed us to better define primary headache syndromes as brain disorders [8].

Several decades ago, the predominant theory of headache was based on a vascular hypothesis and any headache with a "throbbing" pain quality was defined as "vascular headache" [9].

Early imaging studies [10–13] have been performed on patients with migraine with aura (MwA) to explore the theory suggesting that cortical spreading depression (CSD), a suppression of cortical activity advancing at about 3 mm per minute over the cortex [14], was the electrophysiological correlate of visual aura in humans. Indeed, the pioneer Olesen's study [10] by means of single photon emission computerized tomography (SPECT), showed that unilateral, occipito-parietal oligaemia during the aura was preceded by hyperaemia. Furthermore, oligaemia may spread anteriorly and severe headache could occur during this oligaemic phase. Today, it is well-know that the oligaemic phase persists well into the pain phase supporting the concept that vasodilatation could not explain the pain during migraine attack [15, 16].

These imaging findings, far from a theoretic speculation, have had a great implication in clinical practice, suggesting for example to avoid triptans during migraine aura, because aggravating cerebral vasoconstriction in the oligaemic phase of aura could enhance the risk of ischaemic stroke in migraine patients [17].

Although previous findings on CSD have been confirmed by other SPECT studies, in the last decades positron emission tomography (PET) and functional MRI (fMRI) have been subsequently used to clarify the complex pathophysiology of migraine without aura (MwoA). Early PET studies [18, 19], performed in a series of patients with MwoA both during spontaneous unilateral migraine headaches and again after effective treatment of the headaches, have shown an increased regional cerebral blood flow (rCBF) in the medial brainstem contralateral to the headache as well as in cingulate, auditory, and visual association cortices. Successful treatment of the headache with sumatriptan resulted in a normalization of rCBF in cortical areas but did not reverse the brainstem CBF increases. The active areas in the dorsal midbrain and dorsolateral pons suggest a pivotal role of the brainstem in migraine pathophysiology and this activation pattern provides a very robust marker of migraine. These findings led the authors to propose that a "generator" located within the superior brainstem might initiate the development of migraine headache. Subsequent imaging studies have replicated and extended these findings and now it seems clear that a brainstem activation is highly specific to migraine [20–22], implying that the activation is involved in the pain process either with a permissive or a triggering mechanism.

The crucial role of brainstem in migraine pathophysiology has been also confirmed by different non conventional imaging techniques. Indeed, a voxel based morphometry MRI study [23] has demonstrated an increased periaqueductal grey matter (PAG) density, while a perturbation of iron homeostasis in the PAG has been evidenced in migraine patients by MRI iron-susceptible sequences [24].

Taken together, these imaging data indicate that different brainstem structures may participate in headache pathogenesis, probably in a dysfunctional mode, either by lowering the threshold, which makes the system hyperexcitable, or by decreasing the inhibitory nociceptive pathways [8].

More precisely, modern neuroimaging techniques suggest that a central and peripheral activation, starting from the brain and involving the trigeminovascular reflex may represent a key step in the pathophysiology of migraine [25, 26].

Today, neuroimaging is constantly and dramatically improving. However, many of the questions about cerebral networks and their functions in headaches are strictly dependent on the refinement of neuroimaging technology, such as PET and blood oxygenation level-dependent (BOLD) fMRI. The latter has some crucial advantages over PET: (1) PET relies on the injection of radioactive tracers, whereas fMRI is entirely non-invasive, and (2) fMRI has a higher spatial resolution and, especially with an event-related design, a superior temporal resolution [22].

Oxygenated hemoglobin (diamagnetic) differs in its magnetic characteristics from deoxygenated hemoglobin (paramagnetic). Because of neurovascular coupling in the brain, the blood flow and thereby oxyhemoglobin content usually increases with increasing neuronal activity. Finally, changes in neuronal activity can hence be visualized by changes in the BOLD contrast [27].

Therefore, BOLD-fMRI studies have lately provided new insights into functional organization of pain processing networks in patients with migraine during experimental induction of head pain [28–30].

During the last years, researchers have extensively used fMRI techniques to investigate the neural basis of pain perception in migraine patients and shown cerebral activity within a very wide array of subcortical and cortical brain structures [31, 32] by using different nociceptive stimuli. Since the pioneer application of nitroglycerin [21] or capsaicin [33] to the face (within the receptive field of the trigeminal nerve) in patients with migraine, several noxious stimuli such as electrical stimulation of the skin [28], heat [29], cold [34] or mechanic pressure [35] have been used in fMRI studies [36].

More recently, brain imaging of pain in patients with migraine has been performed by instruments characterized

from a good-established and modifiable quality and intensity of pain stimulus revealing that a specific matrix of brain areas is activated in response to trigeminal or other sensitive nerve painful stimulation [29, 30].

By doing so, it was possible to visualize the so-called "pain-matrix" [37]. This "matrix" comprises most consistently, the thalamus, insula, anterior cingulate cortex (ACC), prefrontal cortex, primary and secondary somatosensory (S1–S2) cortices as well as the cerebellum [38, 39], each with specialized sub-functions [40] to encode different aspects of the pain experience. For example, sensory-discriminative aspects of pain perception are often thought to be independently and specifically represented in S1 and S2, (constituting ''lateral pain system'' or ''somatosensory node'') while affective aspects of pain perception, such as emotional response to pain, would be represented in medial brain structures such as the ACC (constituting the ''medial pain system'' or ''affective node''), other than to anti-nociceptive mechanisms [30].

Nevertheless, the emergence of pain would not result from the activation of one or more specific brain areas but it would emerge from the flow and integration of information among these areas [37, 41, 42].

This central network of brain structures involved in pain transmission and processing is under a dynamic top–down modulation by anti-nociceptive brain mechanisms that are also associated with anticipation, expectation and other cognitive factors [30].

Finally, although fMRI provided important insights into the pathophysiology of migraine, we are still far away from discovering the "primum movens" of migraine attacks, most likely because migraine is a complex disorder in which no single factor or structure plays a key role [43–45].

Further imaging studies may reduce the inherent variability of functional studies, and thereby decrease confounding factors in the interpretation of the results.

In future, the possibility of using fMRI, to explore migraine patients' brain before the onset of the headache pain may provide valuable information of the earlier events that activate the pain system [45, 46].

Conclusion

Recent years have seen rapid growth of neuroimaging methodology which has provided new insights into functional brain organization of migraine patients. However, fMRI has today little or no value in clinical practice. In this context, clinicians are crucial, since without a proper clinical selection neuroimaging studies could generate inconclusive results. Likewise, we argue that functional neuroimaging is crucial for clinicians in order to further elucidate pathophysiological mechanisms underlying this complex and often disabling disease and to provide new therapeutical approaches for migraine patients [45].

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

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From neuroimaging to clinical setting: what have we learned from migraine pain?

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Abstract In the last 15 years, the neuroimaging of patients suffering from migraine with or without aura has improved our understanding of the mechanisms underlying the pathophysiology of the disease. A great number of studies based on modern imaging techniques, such as structural imaging and functional imaging emphasize that in migraine patients suffering from repetitive pain attacks, both significant abnormalities of function and diffuse structural changes of brain white and gray matter become striking features of the disease. The hypothesis that migraine pain is due to a global brain disorder with substantial brainstem involvement leading to secondary blood flow changes in the posterior circulation is reinforced by several elegant studies. Clinical application of functional imaging findings in migraine is yet to be considered, since the specificity of some results has to be determined. Nevertheless, functional MRI techniques have a vast potential for exploring the pathophysiology of pain in migraine patients.

Keywords Migraine · Magnetic resonance imaging · Structural imaging · Functional imaging

Introduction

Migraine is a chronic disorder characterized by recurring attacks of severe headache. Although not life-threatening, migraine confers disability and bears a major socioeconomic burden. The complex pathophysiologic mechanism that underlies the disease is not quite understood and clear markers of brain involvement are missing. The application of structural and functional magnetic resonance imaging (MRI) techniques has provided new insights into the distribution and extent of central nervous system (CNS) involvement. The understanding of brain disorder in migraine has been advanced using these new MRI techniques, giving us some features that might help to better understand the relationship between abnormalities of function, structural change and pain modalities.

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Structural imaging techniques

The application of quantitative non-invasive MRI techniques demonstrated that patients with migraine might have structural brain abnormalities that extend beyond lesions detectable with conventional MRI sequences [1]. Voxel-based morphometry (VBM) is a whole brain method to analyze pre-processed structural MRI data treating images as continuous scalar measurements. VBM allows an automatic identification of the regional distribution of gray matter (GM) density (thus avoids observer bias). In migraine patients without [2] and with [3] white matter hyperintensities, decreased GM density has been detected in several areas of the temporal, parietal and frontal lobes. On the contrary, an increased GM density was evaluated in the dorsolateral pons and in periaqueductal gray (PAG) [3]. These findings were replicated by other studies [2, 4, 5]. Thickening of the somatosensory cortex and visual processing areas was also defined [6].

Some authors interpret these data suggesting that repeated migraine attacks over time might result in selective

damage to several brain regions involved in central pain processing. In some way this could support the concept that migraine is a progressive disorder. Longitudinal studies are warmly suggested, considering the brain structural abnormalities as a puzzling data. In fact, the increased density of GM in the dorsal pontine region parallels to the location activated in migraine positron emission tomography (PET) studies [7]. The anatomical co-localization of structural and functional abnormalities raises the question whether the observed features may be due to brain plasticity induced by repeated painful stimulation.

Diffusion-weighted (DW) MRI allows to estimate specific parameters reflecting the microscopic organization of brain measured volume [8]. This technique was able to demonstrate "occult" brain damage in migraineurs. In particular, brain damage in patients affected by migraine extends beyond T2 visible white matter hyperintensities and diffusely involves the so-called "normal appearing" brain matter [9]. In a region-of-interest analysis using tractography based on diffusion tensor MRI reduced fraction anisotropy and higher mean diffusivity was detected in optic radiations in migraine patients with visual aura [10]. A recent diffusion-weighted MRI study observed brain microstructural alterations in right frontal white matter, not correlated with attack frequency and disease duration [11]. The authors speculate about both a maladaptive plastic changes due to repeated pain stimuli in migraneurs or an underlying degenerative process. Admittedly, they state that these findings, given the heterogeneity of the disease and the level of between-subject variability of diffusion parameters, might be only an epiphenomenon reflecting personality traits or changes related to comorbidities.

A recent diffusion tensor (DT) MRI study found that fraction anisotropy value of the corpus callosum in a group of migraine patients with depressive/anxious disorders is significantly lower if compared with a control group and a migraine group without mood disorders. The authors speculate about a possible loss of integrity change or damage of neurofibrotic microstructure in corpus callosum as a neuroanatomical basis of migraine patients complicated with depressive/anxious disorder [12]. A previous study with DT-MRI found increased cortical thickness of motion-processing visual areas (V3A, an area known to be a source of spreading changes involved in visual aura), in association with alterations in superior colliculus and lateral geniculate nucleus (both involved in visual processing). These data derived both from patient affected by migraine with aura and patients affected by migraine without aura. The observed structural changes in the network of motion-processing areas might either be caused by or account for the hyperexcitability that triggers migraine [13].

Functional imaging techniques

Functional MRI (fMRI) and PET have contributed to improve our understanding of migraine pathophysiology. PET studies during spontaneous attacks of migraine showed brainstem activation occurring in the pain phase, persisting after Sumatriptan treatment and headache resolution [14, 15]. In another PET study migraine attacks were provoked, confirming an activation of dorsolateral pontine nuclei ipsilateral to headache pain [16]. Hypothalamic activation in spontaneous migraine attacks without aura was recorded in a PET study [17]. These data could reflect the general processing of painful stimuli or indicate a specific hypothalamic activation as an integrator and trigger of migraine attacks. PET evaluations devoted to cerebral blood study demonstrated haemodynamic changes such as relative bilateral posterior cortical hypoperfusion in migraine without aura, suggesting the possibility that this hypoperfusion could be a consequence of cortical spreading depression (CSD) or a primary neurovascular event [18]. On this hypothesis, the leading event in both types of migraine (with or without aura) could be an oligoaemia triggered by the activation of specific brainstem nuclei. Aura visual symptoms could be produced by CSD derived from oligoaemia in a susceptible brain cortex. In patients affected by migraine and T2 white matter hyperintensities, functional cortical changes particularly involving the sensorimotor network have been demonstrated during a simple motor task [9]. Such functional changes were interpreted as a possible adaptive role due to structural brain damage in migraine.

Using resting state functional MRI, altered connectivity in PAG network in migraine patients was detected [19]. Greater intrinsic connectivity between PAG and both nociceptive and sensory processing pathways, i.e. thalamus, posterior parietal cortex, anterior insula, S1 and M1, was demonstrated, with a positive correlation with disease severity.

Static structural imaging

MRI findings of iron accumulation in PAG correlate with the duration of migraine illness [20]. Decreased T2 signal consistent with increased iron was detected in red nucleus in patients with a migraine history of at least 23 years and aged <50 years [21]. Iron deposition in basal ganglia and pain regulatory nuclei as measured with T2 MRI imaging was evaluated in a group of patients affected by episodic migraine or chronic migraine. Only T2 imaging in the globus pallidus was able to distinguish between episodic and chronic migraine, suggesting the importance of more caudal pain regulatory nuclei in migraine chronicization

[22]. These studies speculate on a possible link between chronicity, disease duration and attack frequency, and brain changes in pain-regulator nuclei.

What does the research teach us?

Research focused on structural and functional imaging has undoubtedly contributed to our understanding of migraine pain. Functional imaging results support the view that migraine is due to a severe episodic disturbance of CNS sensory processing. Brain activation in brainstem structures (with a pivotal role in anti-nociception) is related to pain attack, reinforcing the view that migraine is a subcortical disorder with a crucial brainstem involvement. These data emphasize that migraine has a specific functional neuroanatomical substrate by areas of activation that correlate to the clinical features. The evolution of MRI techniques will help to study much smaller brain areas and to detect slight abnormalities in CNS structures. The development of PET radiotracers which target some particular receptors implicated in pain, such as glutamate and serotonin will help to map the site of brain perturbation in migraine. It is debatable if these advances have a direct clinical application for the diagnosis and treatment of migraine patients. In the future, PET and other neuroimaging techniques will have the potential to be utilized in the important fields of pharmacogenetics, advancing the concept of personalized medicine.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

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From neuroimaging to patients' bench: what we have learnt from trigemino-autonomic pain syndromes

Massimo Leone · Alberto Proietti Cecchini · Angelo Franzini · Giuseppe Messina · Gennaro Bussone

Abstract Trigeminal autonomic cephalalgias (TACs) are primary headaches including cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). A number of neuroimaging studies have been conducted in last decade showing involvement of brain areas included in the *pain matrix.* Apart from *pain matrix* involvement, other neuroimaging findings data deserve special attention. The hypothalamic activation reported in the course of TAC attacks coupled with the efficacy of hypothalamic neurostimulation to treat drug-resistant TAC forms clearly indicate the posterior hypothalamus as a crucial area in TAC pathophysiology. In animal models this brain area has been shown to modulate craniofacial pain; moreover, hypothalamic activation occurs in other pain conditions, suggesting that posterior hypothalamus has a more complex role in TAC pathophysiology rather than simply being considered as a trigger. In contrast, hypothalamic activation may serve as a crucial area in terminating rather than triggering attacks. It also could lead to a central condition facilitating initiation of TAC attacks.

Keywords Neuroimaging · Trigeminal autonomic cephalalgias · Pathophysiology · Trigeminal system · Hypothalamus

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Introduction

The trigeminal autonomic cephalalgias (TACs) are primary headaches characterized by short-lasting unilateral head pain attacks associated with ipsilateral craniofacial autonomic manifestations including cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [1]. These three TAC forms are mainly distinguished by duration of attacks.

Based on the belief that the pain and the autonomic craniofacial phenomena arise, respectively, as the result of simultaneous activation in the brainstem of the trigeminal nerve and craniofacial parasympathetic nerve fibres (the so-called *trigeminofacial reflex*), Goadsby and Lipton [2] proposed the term of TAC for these forms.

Neuroimaging findings [3] and the introduction of neurostimulation for the treatment of drug-resistant TAC forms [4] has greatly improved our understanding of TACs [5]. The clockwork regularity of attacks and seasonal recurrence of cluster periods of CH [6], together with earlier neuroendocrinological studies [7] supported the hypothesis of hypothalamic involvement in this form. So far, neuroimaging studies showed activation of the posterior hypothalamus during CH attacks [8] and increased neuronal density in the same brain area has been shown in CH [9]. Activation of the posterior hypothalamus during CH attacks could trigger activation of the *trigeminofacial reflex.* In the last years neuroimaging studies on TACs as well as data from long-term hypothalamic stimulation have provided hints to a better understanding of the pathophysiology of these primary headache forms. The aim of this paper is to re-examine the central hypothalamic hypothesis in the light of accumulated hypothalamic stimulation and neuroimaging data.

Neuroimaging findings in cluster headache and TACs

In 1998, ipsilateral hypothalamic activation during acute CH headache was demonstrated [8]. The anterior cingulate cortex, the contralateral posterior thalamus, the ipsilateral basal ganglia, the bilateral insulae and the cerebellar hemispheres are also activated [8]. An increased cellular density in the inferior posterior hypothalamus ipsilateral to the pain has been shown [9] and proton magnetic resonance spectroscopy studies have shown decreased *N*-acetylaspartate/creatine–phosphocreatine and choline/creatine–phosphocreatine ratios in the hypothalamus of CH patients compared to migraine patients and healthy subjects [10, 11]. A hypometabolism in the perigenual anterior cingulate cortex, prefrontal cortex and orbitofrontal cortex was found in both cluster period and remission [12]. Again, CH patients showed a disease duration-dependent decrease of opioid receptors in the hypothalamus and anterior cingulate cortex and in the pineal gland as well [13]. Taken together, these data indicate a deranged top-down modulation of anti-nociceptive pathway in CH. This could promote a *permissive* brain condition leading to the initiation of CH attacks (or of cluster periods). On the contrary, one cannot exclude that reduced opioid receptor binding is just the consequence of the pain.

In PH, posterior hypothalamus activation was observed contralaterally to the pain associated with activation of the contralateral ventral midbrain, red nucleus and substantia nigra [14].

In SUNCT hypothalamic activation was firstly reported ipsilateral to the pain [15], but in five patients it was bilateral and contralateral in two patients but no hypothalamic activation was observed in a patient with SUNCT due to a brainstem lesion [16]. Activation of the ipsilateral hypothalamus during attacks was reported in a patient whose headache attacks varied in duration, and could be diagnosed as trigeminal neuralgia, SUNCT, PH, or CH [17].

It is now clear that hypothalamic activation is not specific to CH and TACs: it has been reported in hemicrania continua (contralateral to the pain) [18], in trigeminal neuralgia (ipsilateral) [19], and in migraine (bilateral) [20]. Hypothalamic activation has also been reported in pain conditions others than headache [21, 22].

It is helpful to remind that the hypothalamic brain areas referred to in these various studies are not always identical because stereotactic coordinates differ slightly.

Putative mechanism of action of hypothalamic stimulation

After the observation that the posterior hypothalamus is activated during a CH attack, a novel approach to CH treatment was proposed based on the theory that high-frequency stimulation would inhibit hypothalamic hyperactivity [23]. Hypothalamic stimulation was successfully started in 2000 to treat a chronic drug-resistant CH patient [23]. So far, over 60 chronic drug-resistant CH patients received hypothalamic stimulation at various centres, with relevant clinical improvement in about 60 % of cases showing complete control of attacks in about 30 % [24]. Stimulation must continue for weeks or months before benefit is experienced [25–32], and acute stimulation is unable to improve ongoing CH attacks [33]. Continuous hypothalamic stimulation is also successful in SUNCT [34–36] and in PH [37].

The mode of action of hypothalamic stimulation seems rather complex and not the result of a mere inhibition of hypothalamic neurons, as initially supposed. This is because of inefficacy of acute stimulation and latency of long-term stimulation necessary to improve the condition. The increased cold pain threshold at the site of the first trigeminal branch ipsilateral to the stimulated side suggests that hypothalamic stimulation could exert its effect by modulating the anti-nociceptive system [38].

Another putative mechanism of action of hypothalamic stimulation is a modulation on pain matrix brain areas. In fact, hypothalamic stimulation increases blood flow in brain areas involved in the *pain matrix*, thalamus, somatosensory cortex, precuneus, and anterior cingulate cortex while deactivation occurs in the middle temporal gyrus, posterior cingulate cortex, and insula [39]. Hypothalamic stimulation seems to have the potential to restore a deficient top-down modulation.

The past idea that the hypothalamus is the generator of CH was attractive, but the recent findings and experience with hypothalamic stimulation, suggest caution with this interpretation [4]. Hypothalamic stimulation does not trigger CH pain attacks nor block an ongoing attack: these findings do not support the hypothesis that the hypothalamus is the trigger site in CH. It is possible that the hypothalamus plays a major role in terminating rather than triggering attacks in CH and TACs [4, 39]. Accordingly, the hypothalamus could regulate the duration of a TAC attack giving rise to the different TAC forms mainly distinguished by attack duration [4, 39].

Extensive studies on the autonomic nervous system in hypothalamic stimulated patients suggest that it has little or no role in the mechanism of action of hypothalamic stimulation [40].

Integrating central and peripheral nervous system: the hypothalamus and the trigeminal nerve

Anatomo-physiological studies in rats have demonstrated a direct connection between the posterior hypothalamus and

the trigeminal nucleus caudalis (TNC) through the trigemino-hypothalamic tract (THT) [41]. Peripheral information from trigeminally innervated areas reaches the hypothalamus via the THT. Activity of TNC neurons is modulated by the posterior hypothalamus as shown by changes in neuronal TNC activity by the injection in the posterior hypothalamus of orexins A and B, and the $GABA_A$ receptor antagonist bicuculline. Orexins A and B localize to neurons in and around the posterolateral hypothalamus [42]. These studies point to the role that the posterior hypothalamus has as physiological modulator of TNC neurons [43]. A derangement in the hypothalamic orexinergic system has been invoked in CH pathophysiology and genetic studies give support to this idea [44], even if a large multinational genetic study does not confirm this [45].

In the 1970s Sano et al. [46] successfully treated intractable facial pain with posteromedial hypothalamotomy showing that the posterior hypothalamus is involved in pain control in humans. In recent years, a functional connection between the hypothalamus and the trigeminal system in humans has been demonstrated for the first time: in a $H_2^{15}O$ PET study hypothalamic stimulation was shown to induce activation in both the ipsilateral posterior inferior hypothalamic gray at the site of the stimulator tip and the ipsilateral trigeminal system [39]. The activation of the trigeminal system was never accompanied by headache attacks or autonomic craniofacial manifestations [39]. This observation supports the notion that the trigeminal system activation is not sufficient to explain CH attacks. This is also in agreement with the well-known experience about the persistence of CH attacks notwithstanding trigeminal nerve lesioning [25, 47].

Conflict of interest We declare that we have no conflict of interest.

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The pain in migraine beyond the pain of migraine

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Abstract Migraine is a complex and often disabling brain disorder that affects about 15 % of the population. The diagnosis of migraine is based on clinical features as proposed by the International Headache Society criteria but they are somewhat subjective and arbitrary. Functional neuroimaging of patients with migraine has been recently employed to study the underlying pathophysiology of headache. These studies have suggested that migraine involves functional and structural plasticity of both central and peripheral nervous system. Insights into the fundamental physiology of migraine have been limited by the lack of methods available to detect the pathophysiological background of critical moment of migraine attack onset that is greatly different from the onset of pain or pain phase of a migraine attack. In order to overcome methodological caveats in detecting "migraine origin" or a "migraine generator", functional brain imaging has been lately dominated by experimental acute-pain research. Along this research line functional imaging using experimental pain stimulation have greatly improved our knowledge about physiological or dysfunctional neuronal activity pattern in patients with migraine, but at the same time, it is important to emphasize that experimental pain is different from spontaneous migraine pain.

Keywords Migraine · Experimental pain · fMRI · BOLD · Neuroimaging

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Introduction

Migraine is a complex and often disabling brain disorder that affects about 15 % of the population [1]. The diagnosis of migraine is based on clinical features as proposed by the International Headache Society criteria [2] but they are somewhat subjective and arbitrary. Functional neuroimaging of patients with migraine, rather than improving diagnostic purposes, has been recently employed to study the underlying pathophysiology of headache [3]. These studies have suggested that migraine, as well as other primary headache syndromes, involves functional and structural plasticity of both central and peripheral nervous system [4]. Indeed brain imaging studies have generated several insights into the circuitry that may be involved in the generation and maintenance of pain symptoms in migraine. Along this research line functional imaging using experimental pain stimulation has greatly improved our knowledge about physiological or dysfunctional neuronal activity pattern in patients with migraine.

Among the possible approaches to experimental painful stimulation studies functional magnetic resonance imaging (fMRI) [5] has a fundamental prominence. In the present paper, we will discuss fMRI results that have advanced our understanding on migraine pathophysiology.

fMRI in migraine during experimental pain

In the last decades, blood oxygen level-dependent (BOLD) fMRI, due to its non-invasive nature, has been employed to investigate neuronal mechanisms involved in the migrainous phenomenon [5]. Oxygenated hemoglobin (diamagnetic) differs in its magnetic characteristics from deoxygenated hemoglobin (paramagnetic) and because of neurovascular

coupling in the brain, the blood flow and thereby oxyhemoglobin content usually increases with increasing neuronal activity [6]. Human brain fMRI studies have improved our understanding of brain function in general, and of pain and headache processing specifically [7, 8]. Indeed, since headaches are regarded as brain disorders (until about 10 years ago the central processing of headache was only marginally studied) functional neuroimaging offered much in terms of understanding the neuronal dysfunction that characterizes primary headache syndromes [7]. In migraine, for example, functional imaging has clarified the underlying pathophysiology of the visual aura, whereas in migraine without aura, cortical and sub-cortical activity findings have revealed a dysfunctional pain system [3]. Nevertheless, spontaneous migraine attack mechanisms have been poorly investigated by functional brain imaging.

Insights into the fundamental physiology of migraine have been limited by the lack of methods available to detect the pathophysiological background of critical moment of migraine attack onset that is greatly different from the onset of pain or pain phase of a migraine attack. Indeed, it is remarkable that migraine is far more than an isolated head pain. The key clinical features, other than pain, such as photophobia, phonophobia, osmophobia and nausea argue for a severe episodic disturbance of sensory processing located in the central nervous system. Despite their crucial role in migraine attacks, premonitory symptoms have received little attention in the literature [9]. Moreover, premonitory symptoms of migraine may include a wide and heterogeneous series of cognitive, psychic and physical changes preceding and forewarning of an attack by a few hours to 2–3 days. Unfortunately, clinical studies that have investigated premonitory symptoms of migraine lacked scientific rigor and produced conflicting results, whereas there is an evidence supporting the idea that premonitory symptoms could be used as a phenotypical marker to identify subgroups of migraine patients which could show correlations with specific disease clinical expressions, genotypes, or response to treatments. Therefore, considering the complex phenomenology of a migraine attack, there is the risk that we may not observe, by means of fMRI, a real functional or dysfunctional phenomenon strictly related to migraine origin but a secondary epiphenomenon due to other neuronal mechanisms which may be detectable only in the first phase of migraine, the so-called "prodromal phase". Such epiphenomenon might represent: (1) a compensatory anti-nociceptive systems activation; (2) a reverberating pro-nociceptive mechanism which preserve pain; or (3) a neuronal activity associated with anticipation, expectation and other pain-related cognitive factors.

To overcome methodological caveats in detecting "migraine origin" or a "migraine generator", functional brain imaging has been lately dominated by experimental acute-pain research. At the same time, it is important to emphasize that experimental pain is different from spontaneous migraine pain. First, as above mentioned, migraine is not only pain. Second, migrainous pain seems to be more similar to visceral pain than to somatic pain usually elicited by experimental pain stimulation.

Taking these considerations into account, researchers have become aware that by means of experimental pain stimulation, they can explore pain processing-related cerebral activity in migraine patients but should not draw any firm conclusions about migraine genesis or the existence of an hypothetical central migraine generator [3].

Pioneer fMRI studies have provided new insights into brain functional organization in migraine patients during experimental induction of head pain, in inter-ictal phase, using nitroglycerin or capsaicin applied to the face (within the receptive field of the trigeminal nerve) [10–13].

Ever since, skin sensibility in patients with migraine has been tested by applying different stimuli such as cold and heat stimulation, mechanic pressure stimulation, intramuscular injection of inflammatory substances, or electrical stimulation of the skin [11].

Recently, functional brain imaging of pain in migraine patients has been performed with instruments characterized by a well-established and modifiable quality and intensity of pain stimulus. In fact, by means of new experimental pain models such as heat-pain application with contact thermodes, several studies [14, 15] have revealed that a specific matrix of brain areas is consistently activated in response to trigeminal or other sensitive nerve painful stimulation (Fig. 1). Nevertheless, previous studies that

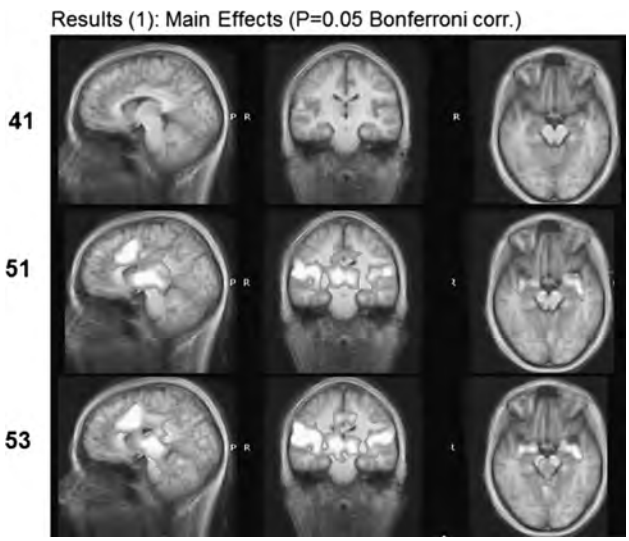

Fig. 1 Main effects of experimental pain stimulation in both patients with migraine and healthy volunteers at different temperatures. **a** 41 °C not painful stimulation; **b** 51 °C moderate painful stimulation; **c** 53 °C severe painful stimulation ($p = 0.05$ corrected for multiple comparisons) (authors' unpublished data)

used thermal heat to initiate painful sensations on the skin of the forehead, maxilla or mandible, accepted the limitations that tactile sensations become intermingled with nociceptive input. This may be considered a minimal bias in studies including a control group, because the same tactile sensation is shared by both patients and healthy controls without differences in activation results.

An alternative method to avoid tactile sensation during painful stimulation is the use of laser where, however, the head coil of the MRI machine makes it difficult to place the laser pointer on the subject's face and bears the danger of accidentally injuring the eyes [16].

More recently, some researchers have used gaseous substances conveyed through an air-proofed tube system that ends in the subjects' nose. This MRI compatible system elicits irritation of the trigeminal nerve by ammonia gas leading to painful sensation, whereas rose odor excited the olfactory nerve and air-puffs are implemented as control condition [16].

Altogether fMRI studies, although using different painful stimuli, have consistently showed an increased sensitivity of migraine patients as compared to healthy controls. Specifically, painful stimulation in migraine patients disclosed a specific and characteristic involvement of pain transmitting structures (the nociceptive system), which include ascending spinal pathways and a central network of cerebral structures. Today, it is well-known that spinal pathways converge onto the brainstem, thalamic nuclei, limbic cortical structures (amygdala, hypothalamus, insular cortex, anterior cingulate cortex, and the sensorimotor [17, 18]). This central network, known as the 'pain matrix', is under dynamic top-down modulation by antinociceptive brain mechanisms that are also associated with anticipation, expectation and other cognitive factors. Indeed, pain is an unpleasant experience and contains emotional feelings involving contextual and cognitive factors, because pain often occurs within a situation that is threatening and stressful [17].

These 'cognitive' qualities and reactions to a situation involving pain have had a great impact on pain fMRI studies results.

To date a key result of fMRI studies in migraine, is that brainstem areas are active during pain and that after successful treatment this activation persists, while it is not present between attacks. The active areas are located in the dorsal midbrain and in the dorsolateral pons. This activation pattern, specifically dorsolateral pontine activation, has also been demonstrated in chronic migraine [4, 18] and thus it may provide a robust marker of migraine disorder [5]. Previous studies showed that dorsal midbrain activation causes migraine-like headache when stimulated in patients with electrodes implanted for pain control [19]. Moreover, patients with lesions in brainstem nuclei (i.e. multiple sclerosis or venous malformation) [20, 21], usually activated during migraine attacks, have been observed to suffer from migraine-like headache.

These data, although of utmost importance, have caused a bias in subsequent fMRI studies using experimental pain model, as they induced either to identify in the brainstem (specifically in pons area) an "a priori" region of interest (ROI) or to use small volume spheres defined on the coordinates of previous studies, sometimes conducted on healthy volunteers. Such ROI-based fMRI studies, on one hand, may corroborate the crucial role of brainstem activation in migraine pain-related mechanisms, on the other they may be inappropriate to explore whole-brain functional changes in cerebral networks, likely involved in migraine pathophysiology.

Regarding laterality, brainstem activations occur predominantly ipsilaterally to migraine side attacks, which suggest that pain lateralization might be a matter of lateralized brainstem dysfunction. However, the interpretation of laterality of brainstem activation by lateralization of the pain during migraine attack is a mystery of migraine pathophysiology. Clinically, despite the strong unilaterality of trigemino-authonomic cephalalgias symptoms, a side-locked unilaterality seems to be a rare phenomenon in migraine thus, lateralization of putative neuronal substrate of a not strictly lateralized clinical pain is an evident interpretative misunderstanding [20–27].

To overcome the above-mentioned methodological limitations, our research group, in a recent fMRI study [28], explored the functional reorganization of pain-related pathways, over the entire brain without any a priori regional hypothesis, in the interictal migrainous phase by means of whole-brain BOLD fMRI during parametric trigeminal nociceptive stimulation using the Contact Heat Evoked Potential Stimulator (CHEPS). All patients were matched for the side predominantly affected by the migraine attack. Nevertheless, we have detected an unilateral left pons activation. It is possible to speculate that activation of pathways involving brainstem is not within the resolution of currently available imaging techniques and, for future researches, close patient selection, intense follow-up and ongoing evaluation will be a crucial issue both to select the most appropriate patients and to extrapolate the experimental results to the clinical arena.

Conclusions

fMRI, with its fast growing developments, gives us an incredible opportunity to learn more about the complex pathophysiology of migraine. Recruiting patients for studies aimed at exploring that the acute migraine phase is certainly not easy, but more studies, looking at different

stages of the migraine attack, will clarify the involvement of several brain structures, especially the brainstem, in this disorder [1]. The interpretation of the biological significance of these various functional changes remains incomplete. Hopefully, a more detailed picture of the migraine neurobiology will emerge from fMRI studies which may eventually lead to better and more rational treatments. Moreover, fMRI techniques are rapidly evolving and soon they will be able to study increasingly smaller brain structures and to detect even subtle abnormalities [5]. Potential future opportunity may lie in the combination of expanding genomic information with detailed fMRI data to evaluate changes in brain areas, mediating neurochemical pathways implicated by genetic polymorphisms linked to specific migraine subtypes [7].

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

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Migraine and depression: bidirectional co-morbidities?

G. Bruti · M. C. Magnotti · G. Iannetti

Abstract Even if the bidirectional co-morbidity between migraine and depression has been supported by epidemiological and genetic studies, many aspects of this association have not been completely understood. This may be due to the heterogeneous character of migraine and depression as well as to their multifactorial pathogenesis. In this review, we have briefly reported the more recent findings published about the co-morbidity between migraine and depression by discussing the above reported issues and the relative clinical and therapeutic implications.

Keywords Migraine · Depression · Co-morbidity · Personality · Stress

Introduction

Migraine is a brain disorder characterized by neurovascular manifestations and affective disturbances.

The relationship between migraine and depression have been extensively demonstrated by epidemiological and genetic studies and some authors support the bidirectional hypothesis of the co-morbidity between these two syndromes [1, 2, 3].

Indeed migraine and depression are both prevalent disorders with a complex categorical classification and with a heterogeneous clinical syndrome.

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The association between migraine and affective disorders is easily noticeable in clinical practice and detectable inside the migraine attack [4, 5].

In this review, we have critically discussed the hypothesized bidirectional co-morbidity between migraine and depression from epidemiological, clinical, and pathophysiological perspective.

Migraine and depression: is there a bidirectional co-morbidity?

Cross sectional and case–control studies showed that depression is almost two time more frequent in migraine than in subjects without migraine. Population-based odds ratio (OR) range from a minimum of 1.8 to a maximum of 4.4 with strongest association for migraine with aura (MA) [6]. Nevertheless, depression has been found associated to migraine (OR 2.2 for migraine without aura and 4 for MA), suggesting a bidirectional relationship between the two brain disturbances [1, 2, 3]. In this view twin and family studies have supported the genetic basis of both disorders and have explained the bidirectional link with the existence of shared genetic factors between migraine and depression particularly for patients with MA [7]. More recently Modgill et al. [8] have found a weaker bidirectional association between migraine and depression that completely disappeared with statistical adjustments for stress and childhood trauma. These findings suggest that the association between migraine and depression may be due more to the presence of environment risk factors common to the two disorders than to the presence of genetic ones per se [8]. In this view the association between migraine and depression would be the consequence of a gene–environment interaction that in turn induces a specific serotonergic

polymorphism [9]. Indeed the dysfunction of serotonergic system has been considered as a potential therapeutic target in both disorders. However, there are no evidences that support the role of selective serotonin reuptake inhibitors (SSRIs) in the prophylaxis of migraine whilst the majority of SSRIs show a similar efficacy for the treatment of depression. That is well known in clinical practice as in clinical research where the improvement of migraine disability and depressive symptoms by using SSRIs are often not correlated [10].

Indeed so far no cohort study (the most suitable design to study a relationship between two variables) has been conducted to support the bidirectional hypothesis between migraine and depression [6].

Unipolar depression in migraine: a bipolar spectrum trait?

In a no blinded cross sectional study, Oedegaard and Fasmer [11] showed that unipolar patients with migraine showed higher prevalence of affective temperaments, seasonal variation, irritability, and agoraphobia than those without migraine. For this reason the authors have hypothesized that migraine in depressed patients may represent a bipolar spectrum trait and have supported the theory of migraine as a marker of "soft bipolarity" [12]. The high prevalence of migraine observed in patients with bipolar disorders (BP) [13, 14], and particularly among BD type II subjects [15] supports this hypothesis and suggests a new interpretation on the co-morbidity between migraine and mood disorders.

Indeed migraine and BD share several clinical features like the co-morbidity with anxiety disorders, suicidal attempts, the episodic course and the response to antiepileptic drugs. In this view does not surprising that the lifetime prevalence of migraine with aura has been found two times higher than that observed in the general population [16].

The concept of migraine as a bipolar spectrum trait in unipolar depressive patients may have some important treatment implications explaining the lack of efficacy of SSRIs and the efficacy of mood stabilizers in the prophylaxis of migraine.

Depressive symptoms: from stressful life events to accompanying symptoms of migraine attack

It is well known that migraine attack is frequently triggered by several conditions like sleep disturbances, food deprivation, and period of stress. These findings support the hypothesis that others brain areas not directly implicated in the control of nociception could be responsible of triggering of migraine attack.

In this view it has been hypothesized that the anatomical and functional link between cerebral areas involved in the stress regulation and meningeal nociceptors may lead to the migraine attack via parasympathetic system [4, 5]. More specifically it has been postulated that the preganglionic parasympathetic neurons of the superior salivatory nucleus (SSN) and the postganglionic neurons of the sphenopalatine ganglion (SPG) could be responsible of intracranial vasodilatation mediated by nitric oxide, vasopressin intestinal peptide and acetylcholine once activated by cortical and sub cortical areas of limbic system involved in the elaboration of emotional signals.

On the other hand, it is well known that also the acute phase of migraine is frequently associated to symptoms like depression, sleepiness, irritability, fatigue, and exaggerated emotional responses. It has been proposed that these symptoms could originate in the limbic structures and hypothalamus under stimulation by trigeminovascular system [5]. According to this physiopathological model the bidirectional link between migraine and depression would be intrinsic to each migraine attack and could be responsible, at least in some patients, of migraine chronification.

Conclusions and remarks

Even if the bidirectional hypothesis of co-morbidity between migraine and depression has to be confirmed by cohort studies, clinical data published in this research field suggest that each headache expert as well as each psychiatrist should be aware for this clinical syndrome in migraine and depressive patients.

Particular attention should be made about the characteristics of mood disorder in migraine with aura patients where a bipolar II depression associated to anxiety disorders have been more frequently observed.

A correct clinical diagnosis would allow a better prognostic evaluation as well as a pharmacological more suitable choice.

Conflict of interest G. Bruti is a Consultant Field Physician of Eli Lilly Italia S.p.A.

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Premenstrual syndrome and migraine

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Abstract Premenstrual syndrome (PMS) includes a wide variety of physical, psychological, and cognitive symptoms that occur recurrently and cyclically during the luteal phase of the menstrual cycle and disappear soon after the onset of menstruation. Headache, often of migrainous type, is one of physical symptoms often reported in the diagnostic criteria for PMS. Menstrual migraine (MM) is a particular subtype of migraine occurring within the 2 days before and the 3 days after the onset of menses. According to this definition, therefore, some attacks of MM certainly occur in conjunction with the period of maximum exacerbation of PMS symptoms. The relationship between MM and PMS has been investigated through diary-based studies which have confirmed the possible correlation between these two conditions. In this paper we provide indications for the treatment of MM, making particular reference to those therapies that may be useful in the treatment of PMS symptoms. Even if triptans are the gold standard for the acute treatment, if symptomatic treatment is not sufficient one can resort to a short-term perimenstrual prophylaxis. Non-steroidal anti-inflammatory drugs have been demonstrated effective in MM prophylaxis. Among natural products there is some evidence of efficacy for magnesium, phytoestrogens, and ginkgolide B. Finally, also a combined oral contraceptive containing drospirenone, taken continuously for 168 days, has shown promising results.

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Keywords Menstrual migraine · Premenstrual disphoric disorder · Premenstrual syndrome

Abbreviations

COC	Combined oral contraceptive
DSM	Diagnostic and Statistical Manual of Mental Disorders
MDQ	Menstrual Distress Questionnaire
Mg	Magnesium
MM	Menstrual migraine
NSAIDs	Non-steroidal anti-inflammatory drugs
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome
RCT	Randomized controlled trial
TTH	Tension-type headache
WHO	World Health Organization

Premenstrual syndrome

Premenstrual syndrome (PMS) includes a wide variety of physical, psychological, and cognitive symptoms that occur recurrently and cyclically during the luteal phase of the menstrual cycle and disappear soon after the onset of menstruation. PMS afflicts 48–90 % of the menstruating population [1]. The severity and frequency of symptoms experienced may differ between each cycle, but their nature is usually stable for each woman. Approximately 40 % of menstruating women experience luteal phase symptoms that are merely bothersome but do not require treatment; for 25 % of women these symptoms are annoying but do not impair functioning; for 10–15 % the symptoms are severe, and among this latter group a smaller number (3–5 %) report significant impairment of one or more areas of daily life [2]. About 80 % of women with PMS report at least one week of

reduced work productivity per month. Furthermore, women with PMS have higher levels of absenteeism as a result of their symptoms than women without PMS [3].

In the tenth edition of WHO's International Classifications of Diseases (ICD-10) [4], the definition of "Premenstrual Tension Syndrome" is included in the Gynecology Section and requires the presence of at least one symptom from a range of physical and emotional symptoms. Unfortunately, the description is somewhat vague because it does not specify a required level of impairment or severity of symptoms, lists few specific symptoms, and does not require prospective confirmation.

The American College of Obstetricians and Gynecologists has proposed a stricter definition of PMS that requires at least one of a list of emotional and physical symptoms to be experienced by women during the 5 days before menses and remit within 4 days of the onset of menses, with no recurrence at least until day 13 of the cycle, in each of three prior menstrual cycles. Identifiable dysfunction in social or economic performance and prospective confirmation for two cycles are required [5]. The emotional symptoms include depression, angry outbursts, irritability, crying spells, anxiety, confusion, social withdrawal, poor concentration, sleep disturbance, thirst and appetite changes, while the physical symptoms can include breast tenderness, bloating and weight gain, headache, swelling of extremities, and aches and pain.

In 1987, the American Psychiatric Association added research diagnostic criteria for severe luteal phase symptoms to the appendix of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R), labeling this condition "Late Luteal phase Dysphoric Disorder".

In 1994, these criteria were revised in the fourth edition (DSM-IV-R) and the definition was changed to "Premenstrual Dysphoric Disorder" (PMDD) [6].

To fulfill the DSM-IV criteria, premenstrual symptoms must occur in the last week before menses and remit within a few days from the onset of the follicular phase. Moreover, they must reach a level of severity that interferes with functioning in work, family, and social relationships. At least five symptoms (including at least one major dysphoric symptom) out of a list of 11 symptoms must have been present in the majority of cycles in the preceding 12 months. Symptoms must be confirmed prospectively by daily monitoring for at least two consecutive symptomatic menstrual cycles and cannot be merely an exacerbation of another disorder. The research criteria for PMDD [6] are listed in Table 1. It is estimated that up to 8 % of women experience PMDD [3].

For some authors, PMDD represents a small subset of women at the extreme end of the PMS severity spectrum. For example, the Royal College of Obstetricians and Gynaecologists divides the PMS into mild, if it does not interfere with personal/social and professional life; moderate, if it interferes with personal/social and professional life, but the woman is still able to function and interact, although perhaps suboptimally; and severe, if she is unable to interact personally/socially/professionally [7]. In this context, PMDD is considered as a research criteria adopted by the American Psychiatric Association for the definition of the severe form of PMS.

Table 1 Research criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) for premenstrual dysphoric disorder (Appendix B)

Premenstrual dysphoric disorder
A. In most menstrual cycles during the past years, five or more of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase and were absent in the week post-menses, with at least one of the symptoms being either (1), (2), (3) or (4):
1. markedly depressed mood, feeling of hopelessness or self-deprecating thoughts
2. marked anxiety, tension, feelings of being "keyed up" or "on edge"
3. marked affective lability
4. persistent and marked anger or irritability or increased interpersonal conflicts
5. decreased interest in usual activities
6. subjective sense of difficulty in concentrating
7. lethargy, easy fatigability or marked lack of energy
8. marked change in appetite, overeating or specific food cravings
9. hypersomnia or insomnia
10. a subjective sense of being overwhelmed or out of control
11. other physical symptoms such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating", weight gain
B. The disturbance markedly interferes with usual activities and relationships with others
C. The disturbance is not merely an exacerbation of the symptoms of another disorder
D. Criteria A, B and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles.

For other authors, instead, PMDD is to be considered as a clinical entity separated from PMS, but the question actually remains unresolved.

Recently, a group of international experts reviewed the guidelines for PMS diagnosis and proposed a list of criteria to be met for diagnosing PMS [3]. "*A woman should be diagnosed as having PMS if all of the following criteria are met*:

1. the symptom(s) occur up to 2 weeks before menses in most menstrual cycles;
2. the symptom(s) remit shortly following onset of menses and are absent during most of the mid-follicular phase of the menstrual cycle;
3. the symptom(s) are associated with impairment in daily functioning and/or relationships and/or cause suffering, emotional or physical distress;
4. the menstrual-related cyclicity, the occurrence during the luteal phase and the absence during the mid-follicular phase are documented by repeated observations by a clinician and/or daily monitoring by the patient;
5. the symptoms are not just an exacerbation or worsening of another mental or physical chronic disorder".

Association between menstrual migraine and premenstrual syndrome

Among the symptoms often reported in the diagnostic criteria of PMS, headache is also mentioned, without specifying whether it is migraine or tension-type headache (TTH). Recently, Fragoso et al. [8] tried to characterize the type of headache occurring in the PMS and to evaluate its exact prevalence. Their diary-based study showed that migraine without aura was the most common type of headache, being present in 60 % of PMS sufferers, followed by TTH (30 %). In the remaining 10 % of the cases the diagnosis was "probable TTH" or there was coexistence of the two types of headache.

Within the clinical picture of migraine without aura a particular migraine subtype should be considered: menstrual migraine (MM), whose attacks occur within a precise time window including the 2 days before and the 3 days after the onset of the menstrual flow. Therefore, some attacks of MM certainly occur in conjunction with the period of maximum exacerbation of PMS symptoms.

The relationship between MM and PMS has been investigated through diary-based studies, which had, however, low sample size.

Beckham et al. [9] evaluated the possible correlation between headache activity and menstrual distress using the Menstrual Distress Questionnaire (MDQ), a 47-item questionnaire which measures seven symptom clusters (pain, inability to concentrate, behavioral changes, autonomic reactions, water retention, negative affect and arousal). Results demonstrated that in women with MM, headache activity was significantly related to both somatic and psychological/behavioral symptom scores during the premenstrual and menstrual phase of the cycle. Moreover, for the psychological/behavioral symptom cluster a significant correlation was also found in the luteal phase.

Facchinetti et al. [10] performed a prospective, diary-based study among women suffering from MM, non-MM or PMS. In migrainous women also suffering from PMS, MDQ scores were similar to those of non-migrainous women in the PMS group. In particular, the premenstrual increase of each cluster of PMS symptoms was identical in MM and PMS subjects with the exception of "negative affect", which in the MM group failed to reach the high score of the PMS group.

These data thus suggest the existence of a possible comorbidity between MM and PMS.

Treatment strategies for MM in the context of PMS

In women suffering from both MM and PMS, headache attacks tend to be more severe, longer and less responsive to treatment and PMS symptoms are also more disabling when compared with women suffering from TTH during the PMS [8].

We will therefore provide indications for the treatment of MM, making particular reference to those therapies that may also control PMS symptoms.

The first approach to MM always consists in identifying the most effective drugs to manage the acute attack. The triptans are considered the gold standard for treatment of MM attacks. In the literature there is evidence by now that almost all commercially available triptans are effective in the specific treatment of MM and recently the use of drugs of association, such as sumatriptan + naproxen sodium and rizatriptan + dexamethasone has also been tested.

If symptomatic treatment is not sufficient, one can consider resorting to a short-term perimenstrual prophylaxis designed to reduce the frequency, intensity, and duration of the attacks and also render them more susceptible to acute treatment. A prophylactic treatment that covers the period of greater susceptibility is feasible provided that three conditions can be verified: (1) that the frequency of extra-menstrual attacks is low, (2) that the menstrual cycle is regular enough, and (3) that the attack occurs at a time sufficiently precise compared with the beginning of the menstrual flow.

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually recommended because they are effective in preventing MM. Moreover, in the case of associated PMS,

they could also be useful above all not only in treating physical symptoms, but also mood symptoms.

In MM sufferers naproxen sodium 550 mg administered twice a day, starting 7 days prior to, and continuing for 6 days after the onset of menses was able to significantly reduce migraine frequency, intensity, and duration, as well as total analgesic consumption as compared with placebo [11]. Mefenamic acid 500 mg three times a day, administered at MM appearance, and continued throughout menstruation, was also able to obtain significant pain relief in 79.1 % of the patients compared with 16.6 % of those taking placebo. About 83.3 % of women in the mefenamic acid group were able to function with or without little effort versus 12.4 % of those in the placebo group. Headaches recurred in all the placebo-treated patients and in 26.3 % of those on mefenamic acid [12].

The use of NSAIDs in the treatment of PMS could be useful in those cases of mild-moderate symptoms, particularly if they are associated with dysmenorrhea, headaches or other musculoskeletal complaints. Three small, randomized, placebo-controlled trials evaluated the efficacy of these drugs administered in the late luteal phase of the menstrual cycle, approximately from 1 week before the onset of menses throughout the first few days of bleeding.

Compared with placebo, naproxen sodium 550 mg twice daily was able to reduce menstrual and premenstrual "pain" and to significantly improve premenstrual "behavioral changes" evaluated on the basis of the MDQ scores [13]. Mefenamic acid 500 mg three times daily was shown to significantly improve premenstrual symptoms, particularly irritability, tension, depression, pain, and headache, when compared with placebo [14]. In a subsequent randomized controlled trial (RCT), the same administration of mefenamic acid was able to reduce both physical symptoms (especially fatigue, headache, and general aches and pains) and mood symptoms (tension, irritability, mood swings) compared with placebo [15].

Magnesium (Mg), an essential element involved in plasma membrane stability, is able to modulate neuronal excitability and vascular tone. In a RCT [16], both the administration of 360 mg/day of Mg pyrrolidone carboxylic acid or placebo starting on the 15th day of the cycle and continued until the onset of menstrual flow were able to decrease the Pain Total Index of headache. The Mg group, however, achieved significantly lower values and fewer headache days compared with the placebo group. In addition, only the administration of Mg was able to significantly improve premenstrual complaints assessed through the compilation of the MDQ.

In another RCT [17], the same administration of Mg during the luteal phase of the cycle was specifically tested for the treatment of PMS. Results showed a significant reduction in the total symptoms score and in the "negative affect" cluster of symptoms in women taking Mg compared with those taking placebo.

A recent RCT tested the efficacy of the association of Mg 250 mg + vitamin B6 40 mg daily, compared with Mg alone or placebo, administered continuously throughout the menstrual cycle. After treatment, the mean score of PMS symptoms significantly decreased in all the three groups. However, the combination of Mg + vitamin B6 was more effective than placebo or Mg alone [18].

The association of magnesium (MgO) 200 mg + vitamin B6 50 mg has been compared with MgO alone, vitamin B6 alone or placebo. No overall differences were found among all the three individual treatments. The only significant effect of the association of MgO + vitamin B6, compared with the two other treatments, was the reduction of anxiety-related premenstrual symptoms [19].

Phytoestrogens are estrogen-like molecules derived from soy that exert estrogenic activity in a limited number of estrogen-target tissues (mainly in the endothelium, brain, bone, intestinal mucosa, kidney, lung parenchyma and bone marrow) but not on the endometrium. This selectivity theoretically confers greater long-term safety than estradiol supplementation, although this has not yet been clearly confirmed.

One RCT evaluated the efficacy of a combination of 75 mg soy extract, 50 mg dong quai extract, and 25 mg black cohosh extract, used twice a day for 24 weeks to prevent MM [20]. The average frequency of MMs was significantly reduced in the phytoestrogen group compared with the placebo group. In a small, open-label study the administration of a combination of 56 mg genistein and 20 mg diadzein per day confined only to the perimenstrual period (from day −7 to day +3) also significantly reduced the number of migraine days after 3 months [21].

As to the use of phytoestrogens in PMS, a RCT demonstrated the efficacy of isolated soy proteins containing 68 mg of isoflavones (genistein, daidzein, equol) in significantly reducing headache, breast tenderness, cramps, and swelling compared with placebo [22].

The use of ginkgo biloba has also been proposed. Ozgoli [23] tested the use of 40 mg leaf extracts in PMS treatment, administered three times a day from the 16th day of the menstrual cycle to the 5th day of the next cycle. There was a significant decrease in the overall severity of both physical and psychological symptoms in both the ginkgo and placebo groups; however the mean decrease in the severity of symptoms was significantly greater in the ginkgo group compared with the placebo one. Moreover, ginkgo biloba extract was significantly effective against the congestive symptoms of PMS, particularly breast symptoms, compared with placebo.

The efficacy of ginkgolide B was confirmed in preventing migraine with aura [24] and pediatric migraine

[25]. From our preliminary experience, the use of ginkgolide B associated with vitamin B2, Coenzime Q10 and Mg, administered from ovulation until the first day of menstruation, is also useful in the prophylaxis of MM, especially if the attacks tend to occur on days −2, −1 and +1 with respect to the onset of menstruation.

The use of the combined oral contraceptive (COC) pill in managing PMS has been tried in order to suppress ovulation and thus the fluctuation of sex steroid hormones. However, initial RCTs have failed to demonstrate any evidence of its efficacy. This was probably because the daily progestogen in the second-generation pills tended to regenerate the PMS-type symptoms. A more recent COC, containing drospirenone (a progestogen with anti-androgenic and anti-mineralocorticoid properties) has been examined for its ability to relieve premenstrual symptoms. Interestingly, a Cochrane review concluded that the use of a pill containing drospirenone can significantly reduce the intensity of the premenstrual symptomatology, especially in women with severe symptoms, i.e. PMDD [26].

The use of COC containing drospirenone in MM sufferers has been evaluated in a prospective cohort study [27]. The purpose of this study was to evaluate the impact on headache of a 168-day extended placebo-free regimen instead of the typical 21/7-day regimen. Results showed a significant reduction in the headache scores during the first month of extended regimen compared with the previous month on the 21/7-day regimen. This persisted throughout the 168-day extended regimen and was associated with a significant reduction in the average number of analgesics taken daily.

Conflict of interest None.

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Migraine and depression comorbidity: antidepressant options

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Abstract Migraine and mood depression demonstrate a high clinical relation and share, also with pain, neurobiological mechanisms, particularly neuro-transmettitorial and phlogistic ones. The choice of an antidepressant to treat both depression and migraine is determined by its efficacy, safety, and tolerability. Antidepressants share comparable effectiveness for the treatment of depressive disorders, but their efficacy on headache varies widely: Tricyclic antidepressants are more effective than SNRIs and SSRIs, but demonstrate dose-limiting side effects.

Keywords Migraine · Mood depression · Antidepressants

Introduction

Migraine and mood depression demonstrate a high clinical relation [1] and people with migraine are about three times more likely to have a major depressive disorder than non-migraineurs [2]. Migraine, depression and pain share neurobiological mechanisms, particularly neuro-transmettitorial and phlogistic ones [3, 4]. The choice of a medication for depression and migraine has to consider several factors, such as: (1) the efficacy on both emotional and somatic symptoms, (2) the safety, related to side effects and to interactions on the disease in itself; and (3) the tolerability that includes the pharmacological interactions and the patient's satisfaction for the cures, strictly related to the adherence to the therapeutic project. Only the fulfilment of all of these aspects can carry out a complete effectiveness of the pharmacological treatment on the depression–migraine association.

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Antidepressants in migraine: prophylaxis and symptomatological treatment

Antidepressants are used by 18 % of control patients and by 39 % of all migraine patients, and nearly half of migraine patients have their psychotropics prescribed by a primary care provider [1].

Although antidepressants share comparable efficacy for the treatment of depressive disorders, their efficacy on headache varies widely [2]. Concerning prophylaxis and treatment of migraine, most tricyclic antidepressants (TCAs) potentiate serotonergic and noradrenergic transmission and block activation of trigeminovascular system [5]. Tricyclic antidepressants, mainly amitriptyline, are more effective than placebo in reducing the frequency of migraine attacks and the prophylactic efficacy increases with longer duration of treatment [6–8]. Their superiority to SSRIs [9] is not confirmed by all studies [7]. Unfortunately TCA side effects are a limiting factor in reaching a dosage that could be effective also for the treatment of mood depression: low dosages allow an effective treatment of migraine and pain, but do not block the vicious circle between depression and pain [4].

The SSRI effectiveness on migraine is still under discussion [7–9]: in a Cochrane review, SSRIs are no more efficacious than placebo in patients with migraine, in a 2-month treatment, but long-term studies are lacking [9]. Furthermore, in some migraineurs, acute administration of SSRIs may cause a worsening of migraine [10], probably

due to a vasodilator response, linked to serotonergic activity on different subtypes of receptors. Some caution and monitoring are warranted for the potential risk of serotonin syndrome with the addition of a triptan to SSRIs/SNRIs [11]. Also SNRIs have been evaluated in migraine patients with or without comorbid depression. Venlafaxine is superior to placebo for migraine prevention [12] and it shows a comparable effectiveness of amitriptyline on pain parameters, but with a better side effect profile [13].

Duloxetine, another SNRI, was proved to be effective in the treatment of chronic migraine both on clinical and antinociceptive mechanisms [14]. In another study on patients with major depressive disorder and concurrent primary chronic migraine duloxetine showed a fast efficacy and a good tolerability [15].

Conflict of interest The author certifies that there is no actual or potential conflict of interest in relation to this article.

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The therapeutic future in headache

Alan M. Rapoport

Abstract There are many categories and individual types of headache and most have a variety of treatment protocols, while a few are best treated by just one medication. This paper will concentrate on acute care medications for migraine and discuss some new and future acute care treatments. There is not much to discuss about prevention, except that onabotulinumtoxinA has been approved for prevention of chronic migraine. Cluster headache will also be discussed, as there are some future treatments for acute care and prevention being studied at present. For the acute care of migraine in the US, we have seven triptans by tablet plus other routes and one non steroidal anti-inflammatory medication approved by the FDA that is currently available (Cambia brand of buffered diclofenac potassium for oral solution). There are several other acute care medications in various stages of development and there are three new methods of administering a triptan and others under investigation. The optimal acute care therapy for migraine should be faster, easier to use and more efficient with fewer adverse events than what is currently available. What follows is a brief review of the status in development for five of the many new acute care medications being investigated: the CGRP antagonist tablet telcagepant, the sumatriptan iontophoretic patch Zelrix, sumatriptan powder for use in the OptiNose apparatus, dihydroergotamine for oral inhalation (Levadex), civamide nasal solution for prevention of episodic cluster headache (Civanex) and sphenopalatine ganglion stimulation for acute cluster attacks in chronic cluster headaches. Other future treatments that will not be discussed include transcranial magnetic stimulation, a 5-HT_{1F} agonist named alniditan, large conductance calcium-activated potassium channel openers, glial modulators or other medications and devices in early stages of development.

Keywords Headache treatment · Migraine treatment · Triptans · Dihydroergotamine · Migraine pipeline · Cluster headache prevention

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Introduction

Migraine is an often disabling disorder which persists for 40–50 years, consisting of attacks of moderate to severe intensity throbbing, unilateral headache, associated with various symptoms (i.e., nausea, vomiting, phonophobia, photophobia, osmophobia and worsening with exertion) and sometimes visual, sensory or speech auras. Migraine affects about 12 % of the population of the US and other Western countries. If we add the patients with chronic migraine and probable migraine it brings the percentage closer to 20 %. Acute treatments for migraine include over-the-counter substances and prescription medications. The categories include simple analgesics, combination analgesics, NSAIDs, prescription analgesics, ergots, triptans and anti-emetics. In Europe and Canada, injectable sumatriptan was the first triptan launched in 1991. In the US, it was available in 1993 and today there are seven triptans available with a variety of formulations including tablets, injections, orally disintegrating tablets and nasal sprays. Although triptans are usually considered as first-line treatment for acute care of migraine attacks, some patients cannot afford them, over one-third of the patients do not respond well to triptans and over half of them are willing to try other treatments than the one they are currently taking.

As for migraine-preventive medications, there are only four approved by the FDA and available in the US at this time, two beta blockers, and two antiepileptic medications. In addition, onabotulinumtoxinA is approved exclusively and specifically for chronic migraine. None of these medications work in more than 50 % of patients and they all have significant possible adverse events. Cluster headache is severe and although we have reasonable acute care medication and oxygen inhalation, we have no preventive medications approved for cluster headache.

Calcitonin gene-related peptide antagonists

Calcitonin gene-related peptide (CGRP) is structurally closely related to calcitonin and amylin and has been intensely studied by Edvinsson since 1983 as a vasodilator and neural agent possibly related to migraine pathophysiology. CGRP is involved in sensory neurotransmission and can be found in most sensory nerves, especially those trigeminovascular afferents in the meninges involved in migraine [2]. It is one of the most potent vasodilators known. CGRP levels measured in the jugular venous system are elevated after migraine and cluster headache attacks, and are normalized by therapy with sumatriptan. Some early researchers thought that CGRP caused migraine pain due to extreme vasodilation and blocking CGRP was considered a goal to prevent migraine pain. It is now understood that migraine pain can be blocked without constricting blood vessels and with only anti-inflammatory action. The vasodilation produced by CGRP is actually a secondary phenomenon and not responsible for migraine pain.

If they gain FDA approval in the US and other countries, CGRP receptor antagonists would be the first non-serotonergic, non-vasoconstricting, migraine-specific medications. CGRP has been shown to have several sites of action including blood vessels, meningeal mast cells and at the trigeminal ganglion, as a facilitator of pain at the synapse of the first and second order neurons in the brainstem, in neurons of the trigeminal nucleus caudalis and in smooth muscle in the wall of the meningeal vasculature; but it probably does not excite or sensitize meningeal nociceptors [3]. CGRP can be blocked by a fragment of the peptide containing amino acids 8–37 (CGRP 8–37).

The first effective CGRP receptor blocker was BIBN 4096 (olcegepant). It was reported that intravenous administration produced headache relief in 66 % of patients compared to 27 % of the placebo patients, without constricting blood vessels in preclinical studies [4]. Telcagepant, previously termed MK-0974, was the first reported oral formulation of a CGRP receptor antagonist. It has been reported to work well in migraine in a phase IIB study published in Neurology and then a robust phase III study published in Lancet [5, 6]. Other trials have been performed. Preclinical data from animal studies show that telcagepant is not a vasoconstrictor and two large multicenter clinical studies show it to be as effective as rizatriptan and zolmitriptan and as tolerable as a placebo. In a recently published article, telcagepant 300 mg was found to be as effective as zolmitriptan with fewer adverse events [6]. This was a randomized, parallel treatment, placebo and active-controlled, double-blind trial performed at 81 sites in Europe and the USA for adults with migraine diagnosed by International Headache Society criteria. Patients with moderate or severe migraine attacks were treated with either oral telcagepant 150 or 300 mg, zolmitriptan 5 mg or placebo. There were five co-primary endpoints: pain freedom, pain relief, absence of nausea, photophobia and phonophobia, all at 2 h after treatment.

According to Dr. Ho's [6] article, 1,380 patients were randomly assigned to receive telcagepant 150 mg ($n = 333$), 300 mg ($n = 354$), zolmitriptan 5 mg ($n = 345$) or placebo ($n = 348$). Telcagepant 300 mg was more effective than placebo for pain freedom [95 (27 %) of 353 patients vs. 33 (10 %) of 343 ($p = 0.0001$)], pain relief [194 (55 %) of 353 vs. 95 (28 %) of 343 ($p = 0.0001$)], and absence of phonophobia [204 (58 %) of 353 vs. 126 (37 %) of 342 ($p = 0.0001$)], photophobia [180 (51 %) of 353 vs. 99 (29 %) of 342 ($p = 0.0001$)], and nausea [229 (65 %) of 352 vs. 189 (55 %) of 342 ($p = 0.0061$)]. The efficacy of telcagepant 300 mg and zolmitriptan 5 mg were much the same, and both were more effective than telcagepant 150 mg. Adverse events were recorded for 31 % taking telcagepant 150 mg, 37 % taking telcagepant 300 mg, 51 % taking zolmitriptan 5 mg, and 32 % taking placebo. The measurement of 2–24 h sustained pain freedom was slightly better numerically for telcagepant 300 mg versus zolmitriptan 5 mg, but there was no statistical difference. A potential benefit of telcagepant and other CGRP receptor antagonists is the lack of vasoconstriction in animal models. This suggests that they may be given to patients with vascular disease, such as coronary artery disease, cerebrovascular disease and peripheral vascular disease. This was not studied in the phase III trials.

During development of this drug, Merck performed a clinical trial to determine if taking a dose of telcagepant twice per day would be a safe and effective treatment possibility for migraine prevention. In that trial, there was some evidence of liver toxicity and the trial was halted. Merck suspended further studies and discussed the situation with the FDA. The result was a plan for further study of the safety of intermittent dosing of telcagepant for acute care of migraine. A large study was performed in 2011 treating patients daily as miniprophylaxis in menstrually

related migraine. Additional liver toxicity and other considerations caused Merck to permanently suspend development of this compound. Another oral CGRP antagonist is currently in multicenter trials by Bristol Meyers-Squibb.

Transdermal iontophoretic sumatriptan patch (Zelrix)

Sumatriptan became the first of the seven triptans to become generic in several countries, which has led to the development of generic formulations of available products and to the design of some novel products containing sumatriptan, including needle-free injection (launched in the USA as Sumavel DosePro), lingual spray, intranasal powder in a novel delivery system (under study as Opti-Nose) and a patch formulation. Naratriptan is also now generic in the US and elsewhere and we may see novel uses of it in the future. One of the more interesting products in development, which may address the unmet need of the nauseated migraineur and/or the patient who does not absorb oral medication optimally during a migraine attack, is a sumatriptan patch. NP101, from NuPathe, is an iontophoretic patch that delivers sumatriptan transdermally. It utilizes a small electric current to drive sumatriptan across the skin delivering 6 or 12 mA/h and maintaining sumatriptan plasma levels above the target level of 10 ng/ml for >7 h [7]. There is a linear relationship between the voltage of the applied current and the amount of drug delivery. As a result, drug delivery is precisely controlled at desired levels, providing consistent therapeutic drug levels. In pK studies, the patch delivered sumatriptan more consistently than either the 100 mg oral tablet or 20 mg nasal spray, providing more predictable delivery by bypassing absorption through the GI tract. At the intended plasma concentrations delivered by the patch, both patches studied were well tolerated. No subject reported atypical pain and pressure sensations or other common triptan adverse events after application of NP101 patches. The most common adverse event for NP101 was application site-related pruritus, which was generally mild and resolved without treatment. No subjects withdrew from the study due to adverse events.

NP101 (Zelrix) may offer significant clinical utility for migraine patients, delivering predictable and consistent levels of medication regardless of the clinical situation. While doing so it circumvents underlying migraine-associated GI disturbances such as nausea and gastric stasis. The patch, which contains a battery, microcomputer and two reservoirs for medication, is easy to use and provides consistent, predictable delivery of desired drug levels over a 4-h period. Drug delivery is programed to stop at 4 h even if the patch remains on the skin. With very few adverse events, Zelrix offers the potential to avoid atypical pain, pressure and other sensations commonly associated with current triptan formulations. In January 2011, after the completion of a successful safety study, NuPathe, the makers of this patch, filed an application with the FDA for approval of the patch in the USA for the acute care of migraine.

The only phase III trial done is entitled, ''The Efficacy and Tolerability of Zelrix, a Sumatriptan Iontophoretic Transdermal Patch, in the Treatment of Acute Migraine.'' It was presented at the Amerian Academy of Neurology in 2010 [8]. It was a randomized, double-blind, placebo-controlled study. Patients had to wait till their migraine attack was moderate or severe in intensity before applying the patch. There were 265 patients who received Zelrix and 265 who received placebo. The intention-to-treat numbers were 226 and 228, respectively. The primary endpoint was pain free at 2 h and the four secondary endpoints were pain relief at 2 h, nausea free at 2 h, photophobia free at 2 h and phonophobia free at 2 h.

The results for pain freedom at 2 h was 18 % for Zelrix and 9 % for placebo which was significant at the $p = 0.0092$ level. The 2 h pain relief rate was 53 % for Zelrix versus 29 % for placebo ($p = 0.0001$). Pain relief was significant at 30 min and was comparable to oral and nasal triptans at 1 h. The three secondary endpoints were all statistically significant. Sustained pain relief results from 2 to 24 h were 34 % of Zelrix patients compared to 21 % of placebo ($p = 0.0015$). Triptan adverse events including atypical sensations and pain and pressure sensations were each 1.7 % compared to 0 % for placebo. Triptan adverse events in product labeling is up to 14 % for oral tablets and 47 % for injections of sumatriptan. Application site reactions for Zelrix were from 7 to 23 % compared to 6–15 % for placebo and no patients dropped out of the study due to adverse events.

There were two 12-month long-term safety trials performed. They too demonstrated strong, consistent efficacy within 2 h, with headache relief in 58 % of migraines treated and pain freedom in 24 % of migraines treated. There was nausea freedom for 79 % of migraines treated. Only three patients (1.6 %) reported a triptan AE. The most common AEs were related to the application site: itching (21.9 %), pain (21.3 %) and hypersensitivity (6.0 %).

NuPathe petitioned the FDA not to have to do a second phase III trial and that request was granted, probably in part due to the availability of extensive data about sumatriptan. Towards the end of 2011, the company was told that they needed to supply more data to the FDA. If this product is approved for migraine, it will be a welcome addition for the treatment of acute migraine, especially when it is important to bypass the GI tract due to nausea and vomiting or lack of efficacy due to poor absorption. It will also be useful in patients who need a triptan but cannot tolerate the

triptan adverse events. It provides more consistent and predictable therapeutic plasma concentration compared to the tablet and nasal spray preparations [9].

Oral inhaler of DHE (Levadex)

Three drugs have been tested in inhalers: dihydroergotamine mesylate (DHE), prochlorperazine and loxapine. The last two are dopamine antagonists, a class of drugs that has been shown to treat migraine acutely when given intravenously. DHE is an ergot that stimulates serotonin and other receptors and has been available in various forms for over 50 years. It still remains the mainstay of treatment at major headache centers in the US when patients have daily headache and have already developed central sensitization and chronic headache syndromes. In that situation, it is usually given three times per day intravenously in small, gradually increasing doses. It is also used in the US and Canada as an acute care migraine medication in a nasal spray form. The intravenous preparation is the most effective, but cannot be used at home; when used in the hospital, it often causes the patient to become more nauseated and vomit even after pretreatment by an antiemetic.

Oral inhalation seems to provide similar efficacy to the intravenous form with the ease of home use and without the intensity of adverse events. Studies were performed with a specially designed device called the Tempo inhaler (MAP Pharma), to deliver DHE deep into the lung automatically after breath actuation [10]. A phase I study of four doses of orally inhaled DHE delivered by the specially designed inhaler versus 1 mg of IV DHE ($n = 18$) was performed. There was a rapid systemic absorption of DHE with a t_{max} of 12 min with a 0.88 mg respirable dose (vs. a 6 min t_{max} with the IV preparation). The systemic levels attained were slightly lower than IV DHE, with the ratio of AUC $0–\infty$ of inhaled versus IV approximately 0.77. The Tempo inhaler is a proprietary, novel, breath-actuated device that is expected to deliver most of the drug deep into the lung, thereby minimizing oropharyngeal deposition and decreasing the urge to cough. Phase II data suggest an onset of action comparable to IV administration of DHE, with both rapid and sustained relief [11].

Phase II results demonstrate that 32 % of patients achieve pain relief as early as 10 min ($p = 0.019$) at 0.5 mg dose. This is somewhat lower than the usual dose IV. DHE delivered by this inhaler was well tolerated in phase II studies with no serious adverse events. There was decreased nausea and no clinically significant changes observed in pulmonary function tests, clinical lab findings, heart rate, blood pressure or respiratory rate.

The phase III trial was conducted under a Special Protocol Assessment agreement with the FDA and reported first at the American Headache Society meeting in 2010 [12]. There were 792 patients included in the primary data analysis of this double-blind, placebo-controlled trial. The patient population studied had more severe migraine pain than expected with 46 % of the patients reporting severe pain and 54 % reporting moderate pain prior to administration of the study drug. There were four co-primary endpoints studied: pain relief was 58.7 % of Levadex patients compared with 34.5 % for placebo ($p = 0.0001$); phonophobia free was 52.9 % of Levadex patients compared with 33.8 % for placebo ($p = 0.0001$); photophobia free was 46.6 % of the Levadex patients compared with 27.2 % for placebo ($p = 0.0001$) and nausea free was 67.1 % of the Levadex patients compared with 58.7 % for placebo ($p = 0.02$).

Pain relief was achieved in 30 min, and this was statistically significant versus placebo. While not statistically significant, 50 % more of the patients receiving Levadex therapy than the patients receiving placebo reported pain relief at 10 min in a post hoc analysis. Levadex was just as effective in treating patients with and without allodynia, early or late in the attack and with or without disability.

Levadex was also found to have a low recurrence rate at both 24 and 48 h irrespective of the definition used. Two large meta-analyses have calculated the cumulative recurrence rate for triptans in general to be 22 and 29 % over 24 h. Using the same definition, this analysis found Levadex to have a recurrence rate of 6.5 % over 24 h and 10.3 % over 48 h. No 48 h recurrence data were reported in the triptan analyses. Factors found to affect the rate of recurrence in the triptan meta-analyses included gender of the patient, age group (below 35 and above 35), and severity of headache pain at the time of treatment (moderate vs. severe). In this analysis, both age and severity of pain at the time of treatment were associated with higher recurrence rates in the placebo group. This data corroborate the clinical finding that the patients treated with DHE acutely usually do not have recurrence of their headache in the next 2 days or considerably longer. This phase III trial and additional trials required by the FDA suggest that inhaled DHE will work quickly, with limited adverse events, even in patients treated late in the migraine attack or those with allodynia and disability. Being able to give DHE to patients at home will make it a very useful treatment for acute migraine attacks.

A randomized, double-blind, placebo-controlled, three-way, crossover pharmacodynamic trial was performed in 24 healthy adults and was designed to compare the acute effects of Levadex, IV DHE and placebo on pulmonary artery pressure by taking regular echocardiogram measurements over a 2-h period. The trial compared the pharmacokinetics (pK) of Levadex and IV DHE and its metabolites, the effects of both routes of delivery on

cardiac function, including echocardiograph findings, 12-lead ECG, and vital signs. In addition, the trial evaluated the pharmacodynamics and pK of two doses of Levadex administered 2 h apart as compared to a single dose of 1.0 mg IV DHE. There was no statistically significant difference between the Levadex and placebo groups in the primary endpoint of pulmonary artery pressure over 2 h after administration.

A clinical trial was performed comparing the pK and safety of Levadex orally inhaled migraine therapy with intravenous DHE in smokers and non-smokers. The trial was designed to measure whether systemic absorption and exposure in smokers is greater than in non-smokers. The trial included healthy adult volunteers, of whom 23 were smokers and 24 were non-smokers. Levadex was well tolerated and no drug-related serious adverse events were reported. In the trial, the systemic absorption of Levadex was not higher and systemic exposure to DHE was not greater in smokers than in non-smokers.

A randomized, double-blind, placebo-controlled, three-way, crossover trial in 54 healthy adults compared the acute effects of a supra-therapeutic dose of Levadex (approximately three times the anticipated commercial dose), oral moxifloxacin (400 mg) and placebo on the cardiac QT interval as measured by electrocardiogram. Moxifloxacin is a positive control known to increase the QT interval. Results of the trial showed that a supratherapeutic dose of Levadex does not increase QTc intervals.

A recent post hoc analysis of the phase III trial demonstrated that Zelrix works very well versus placebo when given late in the migraine attack. For treatment given 8 h after an attack began, Levadex produced headache relief in 49 % of patients versus 24 % for placebo, and pain freedom in 19 versus 9 % for placebo. These and other differences were statistically significant.

Unique nasal powder delivery system of sumatriptan (OptiNose)

There is a new bi-directional, breath-activated delivery system for sumatriptan powder delivered into one nostril called OptiNose. It consists of a mouthpiece and a sealing nozzle which fits into one nostril. The patient blows hard into the device which causes the soft palate to rise, isolating the nasal cavity from the oropharynx. As the patient continues to blow, the device releases a fine powder of sumatriptan deep into the nasal cavity on one side. The drug coats most of the nasal mucosa and air flow carries it through a posterior communication between the two nasal passages to the other nostril and forwards, causing it to coat the second nostril. This improved deposition of drug throughout the nasal cavity speeds delivery to the nasal vasculature and increases absorption. Traditional nasal delivery methods deliver much of the dose anterior to the nasal valve and low in the nasal cavity. A large percentage of the dose is then swallowed and absorbed slowly via the GI tract.

In a phase I study, OptiNose proved to have more extensive absorption across the nasal mucosa than the existing sumatriptan liquid nasal spray device on the market [13]. A phase II study was designed to evaluate the efficacy and safety of a single dose of 10 or 20 mg of a powder formulation of sumatriptan delivered with the OptiNose device in comparison with placebo, in 117 adults with a moderate to severe intensity migraine attack [14]. In terms of efficacy, a greater proportion of subjects who received sumatriptan 10/20 mg were pain-free at 2 h compared with those who received placebo 54/57 versus 25 % (number needed to treat = 3.1/3.4, $p = 0.05$). Pain relief at 2 h for the two doses was 84/80 versus 44 % (number needed to treat = 2.5/2.8, $p = 0.001$). Pain relief was noted as early as 60 min (73/74 vs. 38 %, $p = 0.01$) and at 48 h, sustained pain-free results were impressive (47/49 vs. 27 %, number needed to treat = 4.55/5, $p = 0.05$). The most common adverse event following sumatriptan delivery was dysgeusia, or metalic taste, in 10 % of subjects receiving the 10 mg dose and 13 % receiving the 20 mg dose. No significant adverse events occurred. Specifically there were no cases of chest discomfort or pain, paresthesia or asthenia in the active treatment groups.

When the company completes its phase III trial, if it reaches its primary endpoint with few adverse events, it will apply to the FDA for approval for treating migraine acutely.

Civamide nasal solution for prevention of episodic cluster headache

Cluster headache is probably the most severe pain that headache specialists encounter and there is no approved preventive medication. Many have been tried and there is good evidence that high doses of verapamil often work, but it comes with possible systemic adverse events, especially heart block, constipation and pedal edema. Many other medications have been used, but most have even more adverse events and a lower level of efficacy. For many years, Winston Pharmaceuticals has been studying Civanex, which is civamide nasal solution (*Z*-8-methyl-*N*-vanillyl-6-nonenamide, zucapsaicin), a synthetically produced proprietary new chemical entity in a concentration of 0.01 %. Civamide, a TRPV-1 receptor modulator, selectively depresses activity in type-C nociceptive (pain) fibers and causes a release and subsequent depletion, with a

desensitization to further release of neuropeptides, including substance P and CGRP, that may be responsible for initiating episodic cluster headache. The release of noxious chemicals causes a burning in the nose that begins to disappear over a few days at about the same time that the cluster pain recedes. In clinical trials, after a single week of treatment, there was a decrease in cluster pain of approximately 70 vs. 35 % in the control group by the third week post-treatment, as shown in a meta-analysis of two available studies. As Civanex is not systemically absorbed, treatment does not produce systemic adverse side effects or any interactions with other medications for episodic cluster headache or other medical problems. To date, up to 1,600 patients have been treated with civamide in phase I to phase III studies for several indications using various routes of administration including a patch, nasal spray, oral capsule, and topical cream. The only significant adverse event has been localized burning sensation at the application site.

In 2002, a paper was published based on a trial done at 14 centers showing that 50 μg of civamide was modestly effective in the preventive treatment of cluster headache [15]. In a larger unpublished study of 112 enrolled patients, civamide decreased cluster headache but the p value just missed significance in the mean percent change from baseline in the number of headaches per week, possibly because the control liquid contained saline and may have helped decrease cluster pain.

The meta-analysis of these two studies demonstrated statistical significance after 3 weeks compared to baseline with the primary endpoint versus placebo. The study was statistically positive at $p = 0.0312$. The company is confident that, using only the vehicle as control, their next large study will show positive results leading to approval for prevention.

The FDA has approved a Special Protocol Assessment for a Phase III study and issued a written agreement that if the next study is robustly positive, it would be the final clinical study necessary for approval of Civanex for the prevention of episodic cluster headache. This study is in the planning phase and may begin in 2012 in the US and Europe.

Sphenopalatine ganglion stimulation for the acute treatment of attacks in chronic cluster headache

Chronic cluster headache is often resistant to all attempts at treatment and patients are besides them selves taking too many opioids and other strong medication with little relief. For many years, the sphenopalatine ganglion has been implicated in cluster headache and has been removed, ablated, anesthetized and cocainized with variable relief. A small company named Autonomic Technologies, Inc. in California has studied implantation of a tiny, wireless electrode onto the ganglion, with activation of the electrode remotely at the time of each cluster attack. The electrode is placed on the ganglion through an in-office procedure under local anesthesia. The electrode is turned on and off by the patient via a remote device held over the cheek. The first sham-controlled, multicenter study is being performed in Europe at several centers and should be reporting results this year. All patients are implanted but for some period of time there is only sham stimulation. A previous small study was performed on six intractable cluster patients and reported on by Tepper and colleagues [16]. They were given electrical stimulation to their sphenopalatine ganglion for 1 h for each spontaneous cluster attack. According to the article, "There were 18 acute and distinct CH attacks with clinically maximal visual analog scale (VAS) intensity of eight (out of 10) and above. SPG stimulation resulted in complete resolution of the headache in 11 attacks, partial resolution (>50 % VAS reduction) in three, and minimal to no relief in four attacks. Associated autonomic features of CH were resolved in each responder. Pain relief was noted within several minutes of stimulation [16]". This preliminary trial led to the multicenter trial that is going on in Europe now. If successful, a similar trial will be conducted in the US.

Conclusion

The six innovative medications and/or drug-delivery systems for migraine and cluster headache above could be approved for use in the US within the next 1–3 years, unless problems arise with the FDA. This is a good situation as each will fill a special niche and be useful in certain specific headache situations.

Parts of this paper were adapted from a previously published article 1 year ago in this journal written by this author [17].

Conflict of interest A. Rapoport is on the Advisory Boards of NuPathe and MAP, he consults for Autonoic Technologies, Inc and Winston and is an author of the Phase IIB study on telcagepant studied by Merck.

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Surgical treatment of primary headaches

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Abstract Neuromodulation for the treatment of drug-refractory cranial neuralgias constitutes an exciting field of research for physicians; in the last decade, several methodologies have been described which could help many patients to exit such desperate conditions; although the exact mechanisms of action of these techniques are still matter of debate, several experimental and neuroradiological modalities can help us to get near the concept of understanding them. In this paper, the authors summarize the most recent surgical procedures used to treat severe and pharmaco-resistant cranial painful conditions, along with brief descriptions of the results obtained in the several published so far.

Keywords Neuromodulation · Deep brain stimulation · Cluster headache

Introduction

Chronic cluster headache (CCH) is the only primary headache in which a clear indication to surgical neuromodulation has been established in the last decade [1].

After the preliminary favourable results of pHyp DBS in CCH patients [2], a new interest developed in neuromodulation applied to the treatment of primary headaches and less invasive procedures have been suggested and tested. The neuromodulation procedures tested in the treatment of primary headache include vagal nerve stimulation (VNS), occipital nerve stimulation (ONS), sphenopalatine ganglion stimulation (SPGs) and stimulation of distal trigeminal terminations in the face subcutaneous layer [3–6]. Our aim is to report the results of DBS and ONS in CCH patients suggesting the guidelines for the treatment of patients refractory to the drug and conservative treatment.

Results of posterior hypothalamus deep brain stimulation (DBS)

The first attempt to treat CCH by neuromodulation procedures was based on neuroimaging and particularly on the observation that a discrete volume of the posterior hypothalamus was activated during the pain bouts in CCH patients [7]. The target of the procedure was the alleged hyperactive posterior hypothalamus (pHyp) and its inhibition was obtained delivering "in situ" high frequency current (180 Hz, 1–3 V, 60–90 μs pulse width) trough deep implanted electrodes. Really, the treated patients underwent a full DBS procedure as in the treatment of Parkinson disease; the only difference was the site of the deep target which is the subthalamic nucleus in Parkinsonian patients and within posterior hypothalamus (pHyp) in CCH patients.

Hypothalamic DBS was first tried in 2002 in a patient in desperate conditions due to the dramatic autonomic involvement and pain [8]. Subsequently, we reported on 16 drug-resistant CCH patients who received hypothalamic implants after a mean follow-up of over 4 years [9]. After the first 2 years, pain abolition or major pain reduction was obtained in 13 patients (83.3 % responders). After 4 years

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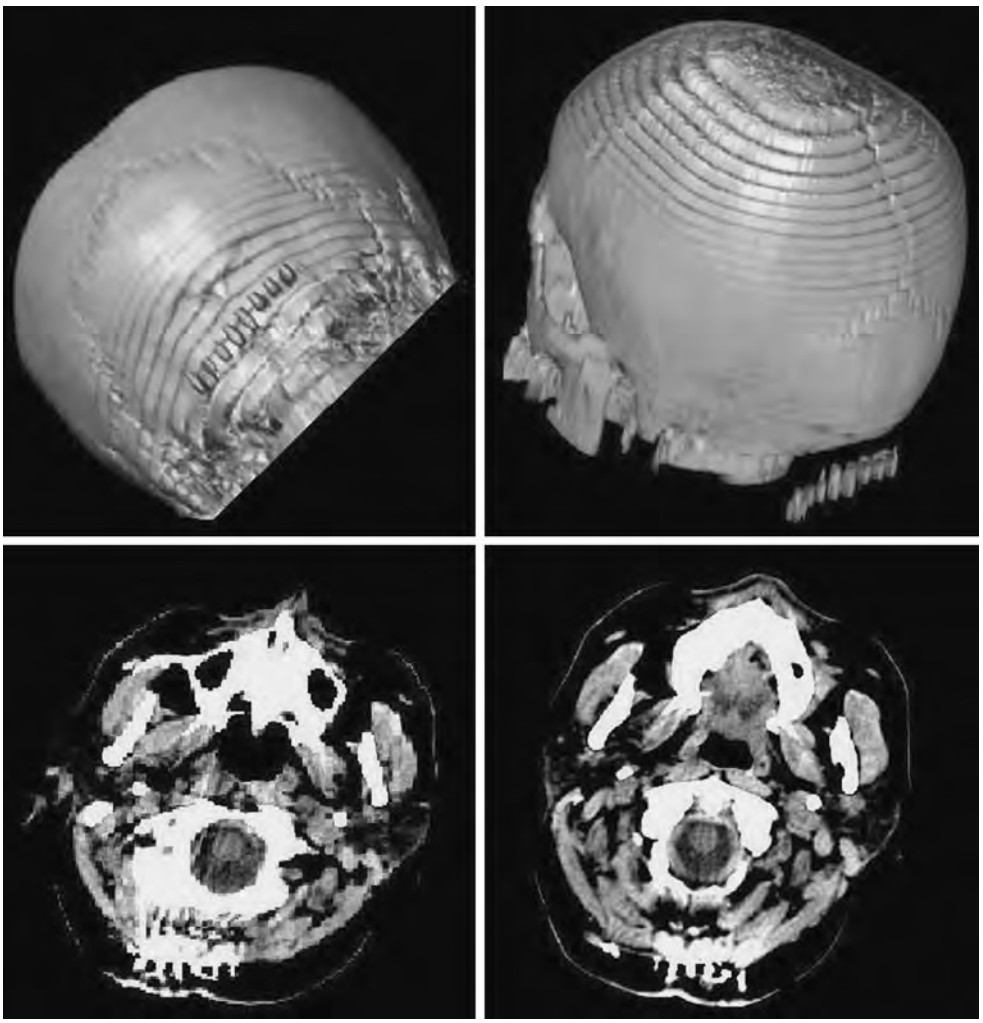

Fig. 1 Post-operative three-dimensional reconstruction CT image (*upper part*) of a patient comprised in our series, submitted to occipital nerve stimulation for refractory cluster headache; as it is shown, in this case, a single median eight-contact electrode was used. *Lower part* Axial images at the level of the electrode

a persistent pain-free state was still present in 10 patients (62 % responders) although four of these also required medical prophylaxis as an add on to control the attacks. Subsequently, hypothalamic DBS became ineffective in three patients despite many changes in the stimulation settings. However, in these patients the illness also changed from chronic to episodic, and they now experience months of complete remission punctuated by periods of brief but typical attacks [10]. Overall about 62 % of patients have obtained significative improvement. In a double-blind, prospective, crossover study, 11 patients from centres throughout France were recruited to assess the efficacy and safety of unilateral hypothalamic stimulation for severe chronic drug-resistant CH [11]. During the randomized phase, there was no significant difference in primary or secondary outcome measures between active and sham stimulation. At the end of the open phase, chronic stimulation had reduced the frequency of their attacks by over 50 % in six patients, three of whom were pain free. There were three adverse events: subcutaneous infection, transient loss of consciousness and micturition syncope. There were no significant changes in hormonal function or electrolytic balance. Although the randomized phase showed no efficacy of hypothalamic stimulation, the open phase indicated long-term efficacy in over 50 % of patients without high morbidity. Of eight CH patients implanted in California [12, 13], five had obtained >50 % reduction in headache intensity or frequency after at least a year, although none were completely pain free. A multicentre study on six CH patients implanted in Germany reported that three patients were almost pain free with treatment failure in the other three [14]. A Belgian centre reported that in four successfully implanted patients, two were pain free and one had improved substantially [15]. One patient from the Belgian series had fatal haemorrhage during surgery. The three patients implanted in Oxford, UK, were

reported as pain free with no side effects after a follow-up of 6 months to 2 years [16, 17]. The latency of chronic stimulation and inefficacy of acute stimulation suggest that the mechanism of hypothalamic stimulation is complex and not the result of simple inhibition of hypothalamic neurons, as supposed initially. At least part of the effect exerted by hypothalamic stimulation could be due to modulation of the antinociceptive system, as suggested by the finding of increased threshold for cold pain at the site of the first trigeminal branch ipsilateral to the stimulated side in chronically stimulated patients [18]. One possible explanation of the role of the hypothalamus in CH and TACs, consistent with the accumulated data on hypothalamic activations, is that this cerebral area plays a major role in terminating rather than triggering attacks. This idea envisages the hypothalamus as regulating the duration of an attack, and the extent to which it does so would give rise to the different phenotypic expressions of the TACs which are principally distinguished by attack duration.

Anyway, pHyp DBS is a powerful therapy in CCH patients when drug treatments and less invasive neuromodulation procedures (ONS and subcutaneous nerve stimulation) fail. The stereotactic coordinates of the posterior hypothalamus referred to the commissural system are: 3 mm lateral, 5 mm posterior to the AC PC midpoint and 4 mm inferior to the commissural plane. The stimulation parameters ranged between 130 and 185 Hz, 60–180 μs pulse duration and 1–4 V amplitude.

Other refractory conditions benefited by pHyp DBS include short lasting unilateral neuralgiform headache with conjunctive injection and tearing (SUNCT) [19], first branch trigeminal neuralgia in multiple sclerosis patients [20] and chronic paroxysmal haemicrania [21].

Results of ONS

Occipital nerve stimulation consists of the stimulation of the greater occipital nerve with paddle- or lead-type electrodes positioned in the suboccipital subcutaneous region and above the splenius capitis' fascial plane; the number of the implanted electrodes (generally one in the midline or two, one for each side) usually vary according to the physician's preference and on the clinical picture of the patient, as do the configuration of the electrodes' themselves, which can have different inter-contact distance and different lengths. Implantation of a single subcutaneous electrode is performed in the midline of the suboccipital region, whereas in the bilateral implants two symmetrical electrodes are positioned 1 cm in the midline below the inion and extending laterally for 4–6 cm, to ensure coverage of the greater occipital nerve's main trunks [22] (Fig. 1). The surgical technique has been described by our group in a previous manuscript [23] and briefly consists of anchoring the plastic tip of each positioned electrode to the underlying muscular fascia with non-adsorbable sutures and of tunnelling the connection cables to the subcostal region, where the internal pulse generators (IPGs) are placed. Clinical indications to ONS are: CCH [24], hemicrania continua [25], transformed migraine [26, 27], cervicogenic headaches [28] and occipital neuralgia [29, 30]. Apart from the latter two indications, the use of ONS for the different types of cranial neuralgias is justified by the presence of a functional unit known as the "trigemino-cervical complex", which comprises the trigeminal nucleus caudalis and the first two cervical spinal myelomeres and in which nociceptive informations of both the suboccipital and trigeminal territory converge, thus stimulation of the greater occipital nerve could modulate the central nociceptive trigeminal neurons through peripheral cervical afferents [31].

Slavin [30] reported a significant improvement of occipital neuralgia in seven out of ten patients previously submitted to trial stimulation, Matharu [32] obtained "good" results in eight patients submitted to ONS (pain reduction ranging from 75 to 90 %); Popeney [26] reported an average improvement of 88.7 % in the Migraine Disability Index (MIDAS) in his series of 25 patients affected by transformed migraine after C1, C2 and C3 electric stimulation; Rodrigo-Royo [28] reported a "good" outcome in four patients submitted to such procedure (C1–C3 electric stimulation) for occipital neuralgia. Trentman [33] reported that 7 out of 8 patients submitted to Greater ONS obtained "fair" or "better" results in terms of reduction of disability.

As far as CCH is concerned, Mueller [34] reported a reduction of frequency, duration, and severity in 90 % of ten patients, with subsequent improvement in quality of life as assessed by SF-36 scale; 70 % of patients in this series were able to reduce the posology of pharmacological treatment, too. Magis [35] reported that seven out of ten patients with drug-resistant cluster headache were responders to ONS after a follow-up ranging from 6 to 30 months; interestingly, in this study, a positive correlation between the responsiveness and the hyperactivity of the perigenual anterior cingulate cortex (PACC) assessed with ^{18}FDG-PET was found. At 6 months, there was a 56 % (range 25–95 %) reduction in the frequency, a 48.8 % (range 20–60 %) decrease in the intensity and a 63.8 % (range 0–88.8 %) reduction in the duration of the attacks. Burns [4] reported that 10 out of 14 patients benefited from the procedure (although in various degrees: percentage of improvement ranged from 20 to 90 %); most of the patients reported relapse of pain attacks after switching off the IPG. de Quintana-Schmidt [36] reported a range of improvement of 25–95 % (mean 56 %) in the frequency and of 20–60 % (mean 48.8 %) in intensity of

cluster headache attacks in four patients submitted to the procedure; all of the patients were reported to "recommend the procedure" in this paper.

Our series of patients submitted to ONS for drug-refractory cluster headache consists of 25 subjects, of which only 20 have a follow-up of more than 3 months. The duration of the illness ranges from 4 to 36 years, and the period of chronicity ranges from 2 to 27 years. 14 out of 20 patients (70 %) responded to the procedure (>50 % reduction in the frequency of pain attacks). Noticeably, whereas all of the responders presented with a minimum of percentage in frequency of the attacks of 90 %, non-responders presented a maximum of percentage in frequency of the attacks of 19 %; there seems to be a "clear" cutoff point between responders and non-responders in our series.

Discussion, guidelines and perspectives of surgical treatment of primary headaches

ONS is the first choice procedure in CCH patients refractory to drugs and conservative treatments. The expected favourable outcome is high (>60 % in our series) and the procedure is minimally invasive. Risks of definitive CNS or PNS lesions are quite zero in ONS patients. DBS is the second choice procedure and carries a certain amount of risks including mortality (<1 %). Both the procedures are based on a definitive neuroprosthesis implant, nevertheless the cost–benefit ratio in CCH patients is clearly favourable to neuromodulation which has been demonstrated to reduce the global costs in term of drugs, hospital admittances, caregivers and disability [37]. Neuromodulation (ONS and DBS) extended more than 80 % the therapeutic possibilities in CCH patients and inspired a huge amount of studies and the development of new devices to treat other primary headaches including migraine and tension type headache. VNS has been used to treat CH patients by Mauskop [3] and also to treat some patients affected by drug-resistant migraine [38]. The recent introduction of transcutaneous VNS which is a non-invasive procedure and can produce neuroimaging alterations and clinical effects similar to VNS [39] may contribute to a better understanding of the indications to VNS in primary headaches. Patients affected by primary headaches may be submitted to long lasting transcutaneous VNS to select patients which could gain stable benefits by surgical VNS. Recently, also the electrical stimulation of the sphenopalatine ganglion has been proposed to treat primary headaches and particularly migraine and CH [6]. In conclusion, reported experiences in CCH patients suggest that central (DBS) and peripheral (ONS, VNS, SPGs and subcutaneous stimulation) neuromodulation will represent an important treatment modality in primary headaches.

Conflict of interest The authors declare no conflict of interest.

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Future trends in drugs for migraine prophylaxis

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Abstract Migraine prevention hinges on a variety of non-specific drugs that mainly reduce neuronal hyperexcitability, the putative pathophysiological hallmark for migraine. The improved knowledge about migraine circuitry and neurobiology has prompted research to develop new specific migraine preventive medications targeted to innovative sites and mechanisms. Drugs designed to inhibit cortical spreading depression, for example tonabersat, might offer a useful option for the management of migraine with aura but not for migraine without aura. Inducible nitric-oxide synthase (iNOS) inhibition seems ineffective as a prophylactic strategy. Results are awaited from recent and ongoing phase II trials with glutamate receptor antagonists, third-generation antiepileptics, melatonin agonists, vitamin D3 and statins.

Keywords Migraine · Prophylaxis · Treatment · Disability

Introduction

Migraine is a common and disabling health problem that affects up to 15 % of the adult population. The accepted criteria for starting migraine prevention require highly frequent or severely disabling migraine attacks or attacks resistant to acute treatment. Treatment aims mainly to reduce migraine frequency by >50 % [1]. The currently available pharmacological options for migraine prophylaxis include a wide array of preventive medications [2]. These drugs act through heterogeneous mechanisms mainly intended to prevent migraine by reducing neuronal hyperexcitability, the putative pathophysiological hallmark for migraine. None of them are specific for migraine, most were discovered by serendipity, many are off patent, and induce adverse effects that impair quality of life and also limit treatment [2]. These drawbacks explain the current need for innovative selective prophylactic drugs. Several compounds targeting new molecular mechanisms and *receptor* binding sites are now in the pipeline [2]. The present paper will discuss current and future directions in migraine pharmacological.

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Current pharmacological approach

First-line treatments for migraine prevention

Antiepileptics

Sodium valproate (800–1,500 mg/day) effectively prevents episodic, chronic and refractory migraine [3], probably by enhancing gamma-aminobutyric acid (GABA)-mediated neurotransmission, attenuating low-threshold T-type Ca^{2+} channels, blocking voltage-dependent Na^{+} channels and reducing plasma extravasation [4]. Common adverse effects are nausea, hair loss, tremor, weight gain and dizziness. Valproate must be used with caution in women of childbearing age owing to reported birth defects in 10.7 % of infants exposed in the first trimester [5]. Another antiepileptic approved for migraine prevention is topiramate. Topiramate, a Ca^{2+} and Na^{+} channel blocker that blocks glutamate, inhibits carbonic anhydrase and stimulates GABA production [4], effectively prevents episodic, chronic, refractory and pediatric migraine at doses ranging

from 50 to 200 mg/day. Common adverse events are paresthesias, weight loss, anorexia, taste disturbances, memory problems, nausea and fatigue [3].

Beta-blockers

Ample clinical evidence supports the efficacy of beta-blockers in migraine prevention (propranolol 80–240 mg/day, timolol 10–20 mg/day, metoprolol 50–200 mg/day, atenolol 50–100 mg/day, nadolol 80–120 mg/day and nebivolol 5 mg/day) [2, 6]. Common adverse effects are bradycardia and hypotension. Beta-blockers reduce firing rates in noradrenergic neurons in the locus coeruleus, regulate neuronal firing rates in the periaqueductal gray (PAG) and probably interact with the serotonergic system by blocking 5-HT_{2C} and 5-HT_{2B} receptors [4]. They seem to prevent migraine by acting on the ventral posteromedial thalamic nucleus thus inhibiting cortical spreading depression (CSD) [4].

Antidepressants

Amitriptyline (25–150 mg/day), desipramine (150 mg/day), chlorimipramine (30–150 mg/day), nortriptyline (100 mg/day) are effective in migraine prophylaxis, probably potentiating 5-HTergic transmission and blocking trigeminovascular system activation [4, 7]. The most common adverse events are sedation, dry mouth and constipation. Venlafaxine 150 mg may be a useful alternative in migraine patients with contraindications to tricyclics [7].

Calcium antagonists

Flunarizine (5–10 mg) significantly reduces headache frequency probably by regulating neuronal excitability and attenuating dural vasodilatation by blocking L-type Ca^{2+} and Na^{+} channels and reducing NO synthesis [4, 8]. The most frequent adverse effects are somnolence and weight gain. Flunarizine must be avoided in the elderly owing to the risk of parkinsonism [8]. Verapamil (80–120 mg) is an effective option in those countries where flunarizine is not marketed [2].

Second- and third-line options

Antiserotoninergics

Methysergide (3–6 mg/day) and pizotifen (1.5–3 mg/day) are effective prophylactic migraine agents that block 5-HT_1 and 5-HT_2 receptors and inhibit histamine release from mast cells [4, 9, 10]. Methysergide should be reserved for severe cases in which other migraine preventive drugs are ineffective and a treatment-free interval of 1 or 2 months should elapse every 6 months to minimize the chronic adverse effects from fibrotic changes in the retroperitoneal, pleuropulmonary, cardiac, and other tissues [9]. The main adverse effects induced by pizotifen are weight gain and sedation [10].

Antihypertensive drugs

Angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers such as telmisartan (80 mg/day), candesartan (16 mg/day) and lisinopril (20 mg/day) provide effective migraine prophylaxis [11–13]. They seem to act by modulating vasoreactivity, altering sympathetic tone, inhibiting oxidative stress, degrading proinflammatory factors such as substance P, enkephalin and bradykinin and probably by modulating the endogenous opioid system [4].

Supplements and herbs

Vitamins and minerals may appeal to patients who want to avoid taking prescription drugs daily. Riboflavin (400 mg/day), coenzyme Q10 (300 mg/day) and magnesium (600 mg/day) are more effective than placebo for a >50 % reduction in migraine frequency [14–16]. Magnesium is an appropriate prophylactic choice for women who are pregnant or trying to conceive. Nutritional supplements are supposed to act on mitochondrial metabolism and to antagonize energetic dysfunction in migraine by stabilizing neuronal function, restoring high-energy phosphate homeostasis and reducing brain oxidative stress [4]. Among herbal remedies, *Petasites hybridus* (150 mg/day) shows an odds ratio (OR) of 2.16 for a 50 % reduction in migraine frequency compared with placebo [17]. No scientific evidence exists to suggest that *Tanacetum parthenium* is superior to placebo for preventing migraine [18].

Botulinum toxin A (BTA)

The use of BTA in headache has gained increasing attention in recent years. BTA is ineffective in tension-type headache and in episodic migraine [19]. Conversely, in chronic migraine prophylaxis, available randomized, double-blind, placebo-controlled trials suggest that BTA is effective. In the PREEMPT1 study, BTA was no better than placebo in reducing the number of headache episodes from baseline [20]. In PREEMT2, BTA significantly reduced headache days versus placebo (9.0 vs. 6.7 days; $P < .001$) [21]. A pooled analysis of data from PREEMPT1 and PREEMPT2 also showed a significant benefit of BTA over placebo for headache days and headache episodes and BTA was also reported to be effective in a subgroup of patients with medication overuse. BTA was

safe and well tolerated [22]. BTA's antinociceptive action in migraine seems to stem from its multifactorial effects on muscle fibers, autonomic fibers, and possibly pain fibers. BTA appears to act on peripheral sensitization by inhibiting substance P, calcitonin gene-related peptide (CGRP) and glutamate release from primary trigeminal and cervical peripheral afferent terminals. Because central sensitization results from ongoing input from peripheral pain fibers, their inhibition would indirectly inhibit central sensitization. BTA is now approved by the FDA for the treatment of chronic migraine and licensed for the same use in the United Kingdom. BTA is a welcome addition to the available *preventive* treatment options for chronic migraine.

Emerging drug targets and new developments in preventive therapy

As our understanding about migraine neurobiology and circuitry advances and research discovers several signaling molecules, molecular genetic strategies have developed highly specific target molecules for migraine treatment. Currently investigated potential targets for migraine prevention include gap junctions, nitric-oxide synthase, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, kainate and pure kainate receptors.

CSD inhibitors

Tonabersat ia a novel benzopyran derivative that blocks CSD, associated NOS activation and cyclic GMP increase in the brain, possibly by binding to connexin and modulating gap-junction function. At the dose of 40 mg/day, tonabersat helps to prevent migraine with aura, reducing median attacks of aura, but has no efficacy on non-aura attacks. Tonabersat might therefore be a useful option for managing migraine with aura but not for migraine without aura [23].

Antiglutamatergic agents

ADX10059 is a metabotropic glutamate receptor 5, negative allosteric modulator (mGluR5 NAM) that induced a significant improvement in the acute treatment of episodic migraine [24]. A large European, phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study investigating the efficacy, safety and tolerability of ADX10059 for migraine prevention has recently terminated. The results are not yet available (http://www.clinicaltrials.gov). Perampanel, a new oral antiepileptic agent, is a potent, non-competitive and selective AMPA receptor antagonist structurally dissimilar to other AMPA receptor ligands that show antiseizure activity. A phase II, prospective, randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate its efficacy and safety in migraine prophylaxis has been recently completed but the results have not been published (http://www.clinicaltrials.gov).

iNOS inhibitors

Inhibition of iNOS is an intriguing issue for acute or prophylactic migraine treatment, because nitroglycerin (an NO donor) infusion is an experimental human model of migraine. GW274150 is a potent and selective iNOS inhibitor that produces analgesia in animal models of inflammatory pain. Despite high selectivity and potency, GW274150 at doses predicted to inhibit iNOS >80 % was, however, ineffective for acute or preventive migraine treatment, arguing against iNOS as a target [25].

Melatonin and melatonin agonists

Melatonin and melatonin agonists, such as ramelteon and agomelatine might be promising tools in treatment because melatonin shows anti-inflammatory and antioxidant effects, inhibiting NOS activity and dopamine release, stabilizing membrane, potentiating GABA and opioid analgesia, protecting against glutamate neurotoxicity, regulating neurovascular function and modulating 5-HT [26]. Ramelteon, a tricyclic synthetic melatonin analog that acts specifically as an MT_1 and MT_2 melatonin receptor agonist, has been licensed in the US for insomnia. A phase II study in migraine prevention is under way (http://www.clinicaltrials.gov).

Third-generation antiepileptics

Carisbamate was less effective than placebo in a 22-week, double-blind, randomized placebo-controlled trial on 323 migraine patients (randomized 1:1:1:1 to treatment with carisbamate 100, 300, or 600 mg per day, or placebo) [27]. A phase II, multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 100 and 300 mg/day lacosamide for migraine prophylaxis has recently completed. The results are not yet available. (http://www.clinicaltrials.gov).

Other drugs (ongoing clinical trials)

A phase II combined trial of simvastatin (20 mg bid) and vitamin D3 (1,000 IU bid) therapy for prophylactic treatment of episodic migraine and a phase II randomized, double-blind, placebo control trial of milnacipran (50 mg bid) aimed at reducing headache pain in chronic migraine are currently recruiting. (http://www.clinicaltrials.gov).

Conclusions

Because the currently available prophylactic drugs successfully prevent migraine in fewer than 50 % of the patients and commonly induce adverse effects, we urgently need to find more specific drugs with higher efficacy and better tolerability. While studies investigating promising molecules active on new targets go ahead clinical work is still needed. First, we need to characterize the various migraine phenotypes, thus allowing phenotype-driven prevention that could selectively test pharmacological responsiveness in specific patient subsets including dopaminergic migraineurs and migraineurs with unilateral cranial autonomic symptoms [28]. We also need to precisely define pharmacological refractoriness. The proposed definition for refractory migraine (migraine which failed an adequate trial of preventive medicines, alone or in combination from at least 2 of the 4 first-line drug classes) is barely acceptable [29]. Before labeling migraine as refractory we must first make sure that the patient fails to respond to trials with at least all four first-line pharmacological classes. Finally, we need to clinically validate polytherapy in migraine prevention, at least in some patients, aimed at integrated prophylaxis simultaneously targeting the various pathophysiological mechanisms underlying migraine including abnormal cortical excitability, energetic dysfunction, and peripheral and central sensitization.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

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Controversies in migraine: monotherapy

Domenico D'Amico

Abstract Migraine patients with frequent and severe headaches need prophylaxis. The most used approach is monotherapy, i.e. one of the available preventive compounds is prescribed to the patient, testing its efficacy and tolerability during a treatment period of some months. Some clinicians use to add a second (or even a third) preventive compound to improve the effects of pharmacological prophylaxis, using an approach that can be defined as polytherapy. In this paper, the main advantages of monotherapy are briefly reviewed, taking into account several aspects: published evidence on polytherapy; the possibility to evaluate the adverse events of the prescribed treatment and to assess its real efficacy; the possibility of addressing different patient's needs, particularly the treatment of comorbidities and the development of an effective patient–physician communication.

Keywords Migraine · Prophylaxis · Monotherapy · Polytherapy · Combination

Introduction

The management of migraine is an important health care issue due to the severity of pain and the presence of relevant associated symptoms and to the occurrence of attacks for several years in most patients, with relevant impact on individuals and on society. Migraine causes disability in daily activities, leads to diminished quality of life, and is characterised by high societal costs [1–5].

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The treatment of migraine patients includes different approaches: avoidance of trigger factors; non-pharmacological therapies; administration of medications. While all migraineurs need appropriate acute treatments to be used to abort individual attacks, patients with severe and/or frequent migraines require also prophylaxis, which requires daily administration of anti-migraine compounds for long periods to reduce headache frequency and improve functioning [6–12].

Prophylaxis of migraine: monotherapy or polytherapy?

Generally, migraine patients are treated with one preventive compound, chosen by the treating clinician among those which are available, and which is usually prescribed for periods of 3–6 months. The minimum suggested trial to assess the benefits of prophylaxis is in fact 2–3 months [6, 7, 11], although many physicians prefer longer treatment periods, which can give more relevant results, as indicated by recently published trials [13, 14]. After such a treatment period, the same or a different compound can be prescribed for a similar or for longer periods, taking into account the efficacy and tolerability of the first prescription as assessed at follow-up visits. This treatment approach can be defined as monotherapy. On the other hand, in clinical practice, some migraine patients are treated with a polytherapy, or combination therapy, which means that they are given two or more preventive compounds at the same time. The basis of this treatment approach in migraine has been reviewed by Krymchantowski and Bigal [15].

Available guidelines on migraine treatment do not explicitly address the problem of monotherapy/polytherapy. An implicit suggestion for using monotherapy may be viewed in the recommendations included in the

Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting, developed by the US Headache Consortium [7]. When discussing the General Principles of Management of Prevention of Migraine, in the Medication Use session, the Authors give the following indications: "A. Initiate therapy with the lowest effective dose. Begin with a low dose *of the chosen pharmacological agent* and increase the dose slowly…B. Give *each treatment* an adequate trial…".

Different aspects may in fact suggest that polytherapy could have some advantages, the most commonly reported being the following: (a) drugs used in migraine prevention are not effective in all the treated patients; (b) some studies reported that the efficacy of some polytherapies in migraine prophylaxis give better results than those achieved in the same patients when using monotherapy; (c) migraine patients often present with comorbid or coexisting condition which may need the prescription of one or more daily treatments.

The aim of the present paper is to briefly discuss the above reported issues, in order to indicate the main reasons for preferring monotherapy as the preferred approach in the pharmacological prophylaxis of migraine. The focus of the present paper is episodic migraine, while discussion of treatment approaches in transformed or chronic migraine is beyond the scope of this article.

Possible advantages of monotherapy

Published international treatment guidelines and specific reviews include extensive reports about the evidence of efficacy of several anti-migraine compounds, based on several published randomised clinical trials [5–12]. However, clinical experience teaches that no single preventive compound is effective in all patients. According to data from clinical trials, headache response (i.e. the proportion of subjects on the given medication achieving a reduction in migraine frequency >50 % as compared to non-treatment periods) of the available compounds is below 50 %. Thus, a relevant proportion of patients is likely to have an insufficient response with one or various compounds.

Some studies have reported that the association of two different anti-migraine compounds may give better results than those obtained with monotherapy, but evidence on polytherapy of migraine is scarce, and not convincing.

Considering the published papers in which episodic migraine patients were studied, a few reports on this topic are available.

Four studies were open-label: in the first study the combination of a beta-blocker + valproate was effective in a series of patients not previously responding to beta blockers, Ca-entry blocker or valproate [16]; in two other studies the associations of atenolol + nortriptyline + flunarizine, and of beta-blocker + topiramate were reported to be superior to monotherapy with the same drugs when used alone, although statistical analyses were not performed [17, 18]; in a recent study [19] the proportions of patients with headache response were not significantly different when prophylaxis with flunarizine or topiramate in monotherapy, and flunarizine + topiramate in combination were evaluated.

Five double-blind studies have been published. In one study, the combination of propranolol and fluoxetine was superior to monotherapy with one of the two compounds [20], but without significant difference at statistical analysis. No difference in efficacy was evident in other two controlled studies: low doses of propranolol and propranolol + nortriptyline gave similar results [21]; polytherapy was not superior to monotherapy in patients treated with topiramate alone, amitriptyline alone or a combination of these drugs, although combination treatment lead to a higher patient satisfaction [22]. Only a recently published trial both the reduction in migraine days and the proportion of patients with headache response were significantly higher in patients in polytherapy with topiramate + nortriptyline than in those in monotherapy with each of these compounds [23]. In another controlled study, a series of patients who experienced at least a 50 % reduction in headache frequency after treatment with either topiramate or valproate, but at the same time reported intolerable adverse events, were switched to the association of the two compounds at sub-optimal daily doses (topiramate 75 mg/day + valproate 500 mg/day): in more than half of the sample tolerability improved "without any decrease in efficacy" [24].

Most of these studies share some characteristics: small clinical samples were enrolled; the studied subjects were often "refractory" to one or more preventive compounds; the drugs which were tested in associations were different across different studies, and some compounds were not among those included in the first or second choice drugs for migraine prophylaxis (such as nortriptyline and fluoxetine) [6, 7, 12].

On the basis of this brief review, it is clear that there is no conclusive evidence of a higher efficacy of polytherapy over monotherapy in the prophylaxis of migraine.

Many migraine patients have comorbid or coexisting conditions: epilepsy, colitis, essential tremor, sleep apnea syndrome, other chronic pain disorders, and, particularly psychiatric (depression, anxiety, bipolar disorder) and cardiovascular (hypertension, Raynaud's syndrome, angina, stroke) disorders [25]. Thus, a proportion of patients with migraine and concurrent medical problems may need two or more drugs. However, the prescription of more than one daily treatment should not be regarded "per

se" as polytherapy of migraine. This situation has been defined as "false polytherapy" in a previously published paper on chronic migraine patients [26], and it may correspond in most cases to what Silberstein et al. [25] defined as therapeutic independence in their review paper on pharmacological approaches to managing migraine and associated comorbidities. This approach is based on the prescription of two or more drugs to a given patient, each compound meant to treat each condition separately. The absolute distinction between patients on a "true" polytherapy (patients in whom all the drugs are prescribed to treat migraine) and those who are on 'false polytherapy'' or are being treated according to therapeutic independence (in whom one compound is prescribed for migraine prevention, and one or more other drugs used on a daily basis aim to treat coexistent conditions) may be not easy in clinical practice with headache patients [26]. The main reason is that many drugs commonly used in migraine prophylaxis are primarily indicated—or have proven efficacy—in other neurological and non-neurological disorders (e.g., valproate for epilepsy, propranolol for hypertension and coronary heart disease).

On the other hand, the fact that most anti-migraine compounds are in fact effective in other conditions may encourage the use of monotherapy, leading to the so-called "two-for-one" strategy. This approach may reduce the number of daily medications in a given patient, limiting possible adverse events, and enhancing patient's compliance and adherence to therapy. However, clinicians must be aware that the use a "two-for-one" strategy may have some risks, which have been systematically discussed by Silberstein et al. [25]. The most common are the risk of treating only one condition; the risk of choosing suboptimal medications. In fact, although one of the two coexisting conditions may be adequately treated with a single compound with potential effects on both migraine and on the other condition, this second illness may require different treatment schedules or daily doses than those used for migraine. Furthermore, the "two-for-one" strategy may lead to the choice of a second- or third-tier line treatment for the coexisting condition or for migraine itself.

Another risk of polytherapy may be related to the problem of adverse events. It is well known that all the drugs commonly used in migraine prophylaxis may cause various side effects [5–12]. In fact, different compounds may be responsible for similar effects: e.g., depression may be caused by propranolol or flunarizine; weight gain may be found in patients on pizotifen, flunarizine, valproate, and amitriptyline. Having a patient on monotherapy enables the physician—and the patient—to evaluate these effects, in order to guide possible changes in daily dose, administration schedule, or withdrawal of a given compound. On the other hand, using polytherapy it could be difficult to assess which of the current treatments needs to be corrected. Furthermore, polytherapy might promote a sum of potential adverse events caused by each of the prescribed compounds.

The use of a single compound may contribute to reduce those factors that are known to negatively influence acceptance of prophylaxis and adherence to the prescribed therapy in clinical practice. This may be particularly evident in those patients who reject the idea of taking a medication each and every day for periods of months, and who are seriously concerned about possible intolerable adverse events [11]. On the other hand, polytherapy may enhance the risk of self-reduction of the prescribed treatments and of withdrawal of medications following trivial side effects.

Concluding remarks

Migraine patients with frequent and severe headaches need daily administration of a preventive compound (prophylaxis). Generally, one preventive compound is prescribed among those that are available, testing its efficacy and tolerability during a treatment period of some months, before prescribing a new therapy, if necessary (monotherapy). However, according to the results of published randomised clinical trials, a considerable proportion of migraineurs who are treated with a given compound may report unsatisfactory results. In clinical practice, some migraine patients are treated with two or more compounds, as some clinicians think that adding a second (or a third) preventive drug may significantly improve the effects of the pharmacological prophylaxis of migraine.

However, polytherapy has not been extensively tested in appropriate clinical trials in migraine patients, and evidence on the real efficacy of the possible association of two or more preventive drugs in migraine prophylaxis is still lacking. For this reason, monotherapy should be the preferred approach in patients with episodic migraine.

As discussed above, monotherapy may have several advantages over polytherapy. It offers the possibility to evaluate accurately the adverse events of a given compound and to assess its real efficacy, allowing the clinician to address the changes needed in the daily dose or in the pattern of administration. Moreover, using a single compound may protect the patient from the potential summing of adverse events or drug interactions.

The results of monotherapy in migraine prophylaxis may be more evident obtained in daily practice as compared to those reported in clinical trials.

The differences in the adverse events profile as well as in the indications for disorders other than migraine which characterise the different anti-migraine compounds give

the chance to tailoring a single preventive compound to the specific patient's needs. Clinicians can obtain optimal results choosing prophylaxis according to patient's characteristics (such as life-style, occupation, preferences), and above all taking into account the possible comorbidities—given the fact that most anti-migraine compounds are effective in conditions other than migraine.

A further aspect that may enhance the satisfaction from a given prophylaxis in clinical practice is the possibility to develop patient–physician communication which has a crucial role in the management of migraine [11]. Also for these aspects, monotherapy seems a better approach than polytherapy, with an easier management of issues related to patient's education and reassurance about possible adverse events and about the daily administration of medications for long periods.

In conclusion, monotherapy seems the most appropriate treatment choice in most episodic migraine patients. Polytherapy should be considered in those patients with proven unsatisfactory response to most available preventive compounds [15, 27]. Before declaring a treatment failure with the monotherapy approach, most—if not all—the first and second line preventive compounds should be tested, and each chosen compound must be used in appropriate daily doses and for adequate time periods.

Conflict of interest The author certifies that there is no actual or potential conflict of interest in relation to this article.

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CONTROVERSIES IN PROPHYLAXIS

Polytherapy for migraine prophylaxis

G. Casucci · V. Villani · D. Cologno · F. D'Onofrio

Abstract Migraine is a chronic neurological disorder with episodic manifestations, progressive in some individuals. Preventive treatment is recommended for patients with frequent or disabling attacks. A sizeable proportion of migraineurs in need of preventive treatment does not significantly benefit from monotherapy. This short review evaluates the role of pharmacological polytherapy in migraine prevention.

Keywords Migraine · Polytherapy · Prophylaxis · Monotherapy

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Introduction

Migraine is a chronic neurological disorder, affecting 10–12 % of the Western population. It is characterized by moderate or severe headaches that last 4–72 h. The attacks are often aggravated by routine physical activity and may be associated with autonomic dysfunction and neurologic symptoms [1]. Migraine is progressive in some individuals [2, 3]. Typically, progression refers to increases in attack frequency over time which may lead to chronic migraine (CM) [4]. About 4 % of the migraine population develops CM [5]. Migraine's progression from an episodic to a chronic form (a condition characterized by headache on 15 or more days per month) is generally influenced by baseline headache frequency, inappropriate use of rescue self medication, inadequate life-style rhythms, and comorbidities. Several psychiatric disorders and medical disorders are comorbid with migraine, and may influence disease progression and preventive strategies [4]. Not readily modifiable risk factors, including age, female sex, race, family history, low educational level or socioeconomic status, genetic factors, and head trauma, may also influence disease progression [6]. Physiologic changes in CM are altered brain metabolism and excitability, and central sensitization of nociceptive pathways [7]. Early therapeutic intervention, before migraine attacks have reached a critical level of frequency (>105 days/year), may serve to prevent the chronification process [8, 9]. The pharmacological treatment of migraine may be acute or preventive, and patients with frequent or disabling attacks often require both approaches [1]. The purpose of migraine preventive therapy is to reduce attack frequency, severity, and duration and to act synergistically with abortive therapy to improve its effectiveness. More broadly, the ultimate goals of prevention are enhance health-related quality of life,

improve the sufferer's level functioning, and prevent disease progression [10]. Preventive medication must be taken daily by the patient with migraine for months or years, in order to obtain a disease-modifying effect [11]. The major medication groups for preventive migraine treatment include anticonvulsants, antidepressants, β-adrenergic blockers, calcium channel antagonists, serotonin antagonists, botulinum neurotoxins, non-steroidal anti-inflammatory drugs, and others (including riboflavin, magnesium, and petasites) [12, 13]. Prophylactic migraine medications are indicated if: attacks occur more than 2–3 times a month; attacks last more then 48 h; migraines are so severe, that the patient is unable psychologically to cope with them; abortive therapy(ies) are inadequate or cause significant side effects; and attacks are associated with prolonged aura [14]. Guideline recommendations suggest that the goal of preventive treatment is to reduce headache frequency by at least 50 %, within 3 months. Typically, therapy is started at a low dose of the chosen drug and increased until the desired therapeutic result or maximum dose is reached or adverse effects develop [12, 13]. Monotherapy is widely favored over polytherapy by neurologists in the first line treatment of migraine [15]. Nevertheless, a sizeable proportion of migraineurs (about 40 %) in need of preventive therapy do not significantly benefit from first monotherapy, i.e., experiencing no meaningful reduction in headache frequency or side effects that impact adherence [16, 17]. In this case, an add-on treatment may be more favorable as second line prevention respect to substituted monotherapy [18].

Refractory migraine (RM) is defined by a poor response to both pharmacological and non-pharmacological treatment. In RM sufferers it is natural to consider a rational combination preventive treatment [19]. A tolerance to the beneficials effects of prophylactic migraine drugs has recently been reviewed [20]. Double-blind randomized controlled trials on migraine preventive treatments, clinical and epidemiological studies of migraine comorbidity, migraine and physiopathological suggestions may support polytherapy for prophylaxis.

Clinical trials

Several open studies showed that combination therapy is effective in migraine patients with incomplete benefit using agents of different pharmacological classes in preventive monotherapy [21–25]. Recently, a randomized controlled trial testing whether combination therapy of topiramate (TPM) and nortriptyline (NTP) was useful in patient who had less than 50 % decrease in headache frequency with the use of a single agent, showed that 78.3 % of patients who received polytherapy had at least 50 % headache reduction as compared to 37 % in monotherapy [26]. In a randomized placebo-controlled trial, Holroyd et al. [27] observed that the addition of combined betablocker plus behavioral migraine management, but not the addition of betablocker alone or behavioral migraine management alone, improved outcomes of optimized acute treatment in frequent migraine. Another double-blind randomized controlled trial showed that a low dose of propranolol (40 mg) was effective alone or in combination with NTP for the preventive treatment of migraine, not resulting in higher intolerance or more frequent side effects [28]. A randomized 1-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis showed that all treatments are effective and have good tolerability. The mean monthly days and severity of headache declined more significant in the flunarizine plus topiramate group. Adding topiramate to flunarizine may reduce the latter's on body weight [29]. The usefulness of combined pharmacological therapy has been confirmed by same observations on neuropathic pain and on epilepsy. In a double-blind crossover trial, the combination of NTP and gabapentin seems to be more efficacious than either drug given alone for neuropathic pain [30]. Several epidemiologic studies in epilepsy showed that patients who failed treatment with initial medication because of a lack of efficacy had a much lower seizure-free rate when compared with rate in patients who had intolerable side effects [31–33]. Possible predictors of an increased likelihood of monotherapy failure in epileptic patients include a history of 10 or more seizures at presentation, a family history of epilepsy, a history of febrile seizures or traumatic brain injury, intermittent recreational drug use, previous or current psychiatric comorbidity, and atypical presentations of idiopathic generalized epilepsy (IGE) [34].

Comorbidities

Migraine is frequently associated with both comorbid and concomitant illnesses that influence treatment strategy. The common illnesses that are associated with migraine and influence its management include comorbid conditions, such as depression, anxiety disorders, epilepsy, sleep disorders, and stroke and concomitant illnesses such as hypertension and obesity [35]. It has been recognized that monotherapy may be preferred for preventive therapy, but clinically this may not always be attainable, especially when two disorders are concomitant. Monotherapy appears to offer some advantages, such as simplifying management, reducing costs, minimizing potential side effects, and eliminating potential drug interactions. However, the scientific rationale for using a "two-for-one" approach in

migraine has not been prospectively tested in controlled trials. Recent studies suggest that using multiple medications (polypharmacy) may confer therapeutic advantages for patients with migraine and other conditions in terms of adequate control of symptoms [21]. The main limitations to use a single medication to treat two separate illnesses include the risk of treating adequately only one condition, risk of choosing suboptimal medication, risk or poor tolerability when a third comorbid or coexistent condition is present, and treatment timelines [35]. Therefore, choice and combination of migraine preventives are also based on the presence or absence of comorbidities.

Pathophysiology

The pathophysiology of migraine is complex, and is only partially known. Central nervous system (CNS) dysfunction is certainly involved in migraine with a pivotal role of the trigeminal system for expression of both peripheral and central symptoms. Derangement in central monoaminergic systems, abnormalities of metabolism of glutamate and GABA, and mitochondrial cellular energy failure are probably the major physiopathological events involved [36, 37]. If the migraine attack depends on a single pathogenetic chain, then monotherapy would be justified, because an effective drug can break the chain. When several pathogenetic chains exist in parallel, grouped in more than one independent or partially independent sequences leading to an attack as occurring in migraine, polytherapy should be more suitable. It is possible that polytherapy could influence different independent elements in the pathogenesis of migraine, i.e., the cortical excitability and brain metabolism [17]. A brain state of hyperexcitability has been postulated to explain the susceptibility to migraine attacks. Cortical spreading depression (CSD), a spontaneous neuronal depolarization moving slowly (3 mm/min) on the occipital cortex, is the most suggestive argument for the brain hyperexcitability [38]. It has been shown that valproate, topiramate, amitriptyline, and propranolol inhibit CSD in rats, which suggests that the most preventive treatments of migraine could act normalizing neuronal firing, and increasing a genetically lowered and environmentally modified threshold for neuronal discharge [39]. A different effect of migraine preventive drugs on CSD has been postulated in rat [40]. A pharmacological add-on mechanism to prolong the excitability-diminishing effects of the transcranial direct current stimulation has been suggested in diseases displaying enhanced cortical excitability, e.g., migraine and epilepsy [41]. It has been hypothesized that some anti-migraine prophylactic drugs (i.e., amitriptyline, candesartan, and magnesium) may also act by restoring central nociceptive dysmodulation [42]. A mitochondrial cellular energy failure in the brain of migraine sufferers has also been hypothesized [43, 44]. Its confirmation is the demonstrated efficacy of some nutritional supplements acting on mitochondrial metabolism, such as riboflavin (vitamin B_2) and coenzyme Q10, in migraine prophylaxis [45]. Different peripheral mechanisms of action of anti-migraine prophylactic drugs have also been hypothesized, particularly in chronic migraine [46].

Conclusion

Monotherapy should be the rule in first line migraine prevention. Nevertheless, clinical data and physiopathological evidences suggest that add-on therapy should be considered in migraineurs who present high disability, concurrent risk factors (not modifiable and modifiable), comorbidities and a history of failed first preventive drug. Further, studies are needed to confirm the superiority of polytherapy versus monotherapy in migraine prevention.

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

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ORAL COMMUNICATIONS

Decision-making deficit in chronic migraine patients with medication overuse

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Abstract Patients with chronic migraine developing medication-overuse headache (MOH) show dependency-like behaviors such as loss of control over analgesics despite adverse consequences on headaches, high rates of relapse after withdrawal from symptomatic medications, and compromised social functioning. Neuroimaging research suggests a common pathophysiology between substance-use disorders and MOH, which involves functional alterations in fronto-striatal networks, particularly in the orbitofrontal region of prefrontal cortex. These findings could explain the impaired decision-making observed in substance-use disorders. We hypothesize that MOH could share fronto-striatal circuit dysfunction and relative decision-making deficit with addiction. We further examine whether this deficit is a persistent cognitive trait or a reversible consequence of medication overuse. This study shows a dataset of 50 patients with MOH before the detoxification. All patients underwent a complete neurological and psychiatric examination. Psychiatric examination consisted of a clinical interview, Structured Clinical Interview for DSM-IV TR Axis II Personality Disorders, Anxiety and Depression Hamilton Scales, Severity of Dependence Scale. The neurological examination included the migraine disability assessment questionnaire. Neuropsychological assessment of fronto-striatal circuits was investigated using the Iowa gambling task (IGT). Twenty patients monitored for any relapse into medication overuse had 12 months of follow-up. Our sample, characterized by high rates of disability and dependency-like behaviors, exhibited a deficit in IGT performance, indicating an overall impairment in decision-making. All the 20 patients showed neurological and psychiatric improvement at 12-month follow-up, notwithstanding the overuse relapse, but a persistent IGT deficit was found. To our knowledge this is the first study that assesses this cognitive function in patients with MOH. Medication-overuse headache seems to share a persistent decision-making deficit with substance abuse that confirms the orbitofrontal cortex hypometabolism described in literature from a neuropsychological perspective. Looking at these shared neurocognitive features, our results suggest that MOH could belong to the addiction spectrum. Fronto-striatal dysfunction could be a premorbid psychobiological condition of vulnerability explaining the clinical onset of medication overuse and recurrent relapses. We propose that IGT could be used to identify chronic migraine patients with higher risk for medication overuse and relapse.

Keywords Orbitofrontal cortex · Iowa gambling task · Decision-making · Medication-overuse headache · Addiction

Abbreviations

MOH	Medication-overuse headache
fMRI	Functional magnetic resonance imaging
OFC	Orbitofrontal cortex
PET	Positron emission tomography
IGT	Iowa gambling task

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Introduction

From 30 to 50 % of chronic migraineurs who, during the natural history of their disease, experience an increase of episode frequency and intensity, start overusing symptomatic drugs for migraine in order to cope with pain and disability. They enter a vicious cycle where overuse of medications no longer controls headaches and becomes responsible of the onset of a secondary headache with variable clinical features, called medication-overuse headache (MOH) [1, 2].

Beyond the necessity of coping with the increased pain and disability, some dependency-like behaviors are being pointed out as possible reasons for medication overuse [3–5]. Loss of control over the use of painkillers despite the adverse consequences on headaches (unmanageability) and high rates of relapse (powerlessness) occur in a high proportion of patients (30–40 % at 1 year, 40–70 % after 4–5 years) [2]. Pharmacological tolerance, cephalalgiaphobia, high rates of disability and compromised social functioning are often observed in these patients. Taken together, these findings brought many authors to consider MOH a bio-behavioral disorder [3–6]. Both the Fuh and Radat studies found around 70 % of comorbidity between MOH and substance abuse according to DSM-IVTR [4, 7].

Chronic exposure to addictive drugs is shown to be associated with impairment of several neural networks, including the fronto-striatal circuit, which involves the prefrontal regions (including the dorsolateral cingulate anterior and orbitofrontal areas), the limbic system (amygdala, entorhinal cortex), and their projections to the ventral striatum [8, 9].

The impairment of this circuit results in prefrontal cortex impairment with a relative dominance of limbic regions on behavior. As prefrontal regions no longer guide the behavior toward controlled, rational and appropriate choices, limbic dominance causes a loss of control, and an increase of impulsivity and semi-automatic actions [10].

In the meta-analysis on impaired decision-making in addicts by Dom et al. [11], ten samples of patients with various substance-use disorders exhibited impairment in decision-making tasks relative to controls.

Some functional neuroimaging studies have investigated the relationship between decision-making deficit and neural activation in different prefrontal areas. Both the fMRI study by Paulus et al. [12] on meta-amphetamine addicts, and the PET study by Bolla et al. [13] on cocaine abusers, gave evidence that the decision-making deficit shown by these samples compared to controls was consistent with both orbitofrontal and dorsolateral prefrontal dysfunction.

A commonality between MOH and addiction arose from a PET study by Fumal et al. [14], who found a persistent hypometabolism of OFC 3 weeks before and 3 weeks after the detoxification in MOH patients, suggesting that this dysfunction might predispose certain migraineurs to MOH and to relapse after the detoxification.

To our knowledge, while various studies have focused on neuropsychology among those with substance-use disorders, this is the first attempt to evaluate decision-making in MOH patients through a neuropsychological task, the Iowa gambling task (IGT).

Designed to assess patients with ventromedial lesions of the prefrontal cortex, this computer-based card task is known to evaluate the decision-making function [15].

The task consists of picking cards from four decks, each of which can give unpredictable rewards or penalties. In order to maximize an initial €2,000 loan of play money, participants need to weigh short-term rewards against long-term losses. In fact, the two risky decks (A and B) give high rewards (€100), but total penalties outweigh them. Otherwise, decks C and D give small but safer rewards (50€). The optimal strategy is to integrate the value of these varying rewards and penalties over time, avoiding the short-term appeal of decks A and B in favor of the slower gain from decks C and D. Performance on the gambling task is evaluated through a net score, which corresponds to the number of cards drawn from the advantageous decks minus the number of cards drawn from the disadvantageous ones. When negative, the net score expresses indeed a decision-making deficit.

Wondering as to whether or not MOH patients would show the same decision-making impairment previously observed in addicts [11], we decided to compare the IGT performances of MOH patients and healthy gender, and age-matched controls. Furthermore, we investigated the nature of this possible deficit, whether this was a temporary consequence of medication overuse or a persistent feature.

Materials and methods

A sample of 50 patients, from 18 to 65 years of age with a history of chronic migraine (i.e., present at least 15 days a month on a regular basis for at least 3 months) and medication overuse (according to the latest ICHD-II criteria, category 8.2.7) [16], were enrolled in the Headache Clinic of the Neurological Institute Carlo Besta in Milan.

The first psychiatric evaluation included: Structured Clinical Interview for DSM-IV TR Axis II Personality Disorders, Hamilton Rating Scales for Anxiety and Depression, migraine disability assessment (MIDAS) questionnaire and severity of dependence scale (SDS).

The MIDAS questionnaire was developed to measure the headache-related disability. It attempts to determine how many days were affected in a patient's life to the point that he/she was unable to function in a usual way. Migraine

disability assessment takes into account the last 3 months when asking the questions [17, 18]. The SDS is a five-item questionnaire, originally created to investigate opiate dependence, recently used in people with primary and secondary chronic headache to detect patterns of medication overuse and dependency-like behaviors [19, 20]. In order to assess decision-making, both patients and healthy age- and gender-matched controls underwent the Italian version of the computer-based IGT [15].

The demographic, clinical, and psychopathological characteristics of the patient population are described as means and standard deviations, and reported in Table 1. Twelve months later long-term monitoring was set up with the same battery of tests in an outpatient regimen in order to detect any relapse into medication overuse and dependence. In the follow-up data elaboration, *t* test and Chi-square were, respectively, used for comparison of continuous or parametric variables (Mann–Whitney and Fisher exact test, as appropriate). Type I and II errors were possible because of the number of subjects and comparisons. In consideration of the exploratory nature of the study, we referred to levels of significance of $P \leq 0.05$, without operating any correction for multiple comparisons.

Results

Of the 50 MOH patients included in the study, most patients had continuous headache with superimposed episodes of acute headache (mean frequency of episodes per month was 21.96 with 6.59 SD) and daily drug intake (mean number of tablets per month was 31.04 with 22.51 SD). The overused medications were triptans alone (20 patients, 40 %), simple analgesics alone or in combination with caffeine (26 patients, 52 %) and triptans plus analgesics (six patients, 12 %).

Twenty-two patients (44 %) and 14 patients (28 %), respectively, had a past and present Axis 1 psychiatric diagnosis (anxiety disorder, major depressive disorder). None fulfilled DSM-IVTR criteria for personality disorders.

The sample was characterized by high rates of disability (mean MIDAS score was 69.60 with 49.18 SD) and severe dependency-like behaviors due to anti-migraine drugs (mean SDS score was 8.73 with 2.23 SD): 47 patients (94 %) achieved an SDS score greater than or equal to 5, the cut off for diagnosing the behavioral addiction for painkillers [20].

Our sample of MOH patients showed a statistically significant deficit in decision-making (mean net score on IGT was −10.40 with 15.82 SD) compared to healthy gender- and age-matched controls (independent sample *t* test with *t* 8.08; *df* 79.6, sig two-tailed 0.000).

The dataset for the longitudinal study is now available for the 20 patients: according to ICHD-II criteria [16], 13 of them (65 %) discontinued medication overuse after the detoxification and restored an episodic migraine pattern; 7 patients (35 %) relapsed into MOH at 12-month follow-up, despite the temporary resolution of medication overuse soon after the detoxification.

Observing the clinical and psychopathological score transition in the follow-up sample regardless of relapse (Table 2), we found very significant decreases in MIDAS score, pain intensity, frequency of episodes, and number of tablets per month. In contrast to this global improvement, the mean net score in IGT performance remained negative (−7.70 with 16.92 SD), with a 1.00 statistical significance in the paired samples *t* test, showing a persistent deficit in decision-making.

Table 1 Demographic and clinical features of medication-overuse headache (MOH)

	Baseline during withdrawal ($N = 50$)			
	Minimum	Maximum	Mean	SD
AGE (years)	23.00	65.00	41.28	9.96
Migraine duration (years)	1.00	60.00	22.13	13.05
Medication overuse duration (years)	0.25	36.00	2.99	6.57
Frequency of episodes per month	15.00	30.00	21.96	6.59
Number of tablets per month	14.00	90.00	31.04	22.51
Pain intensity on VAS	3.00	10.00	7.80	1.64
HAM-A score	0.00	30.00	13.19	7.91
HAM-D score	0.00	39.00	12.60	7.56
Iowa gambling task net score	−52.00	14.00	−10.40	15.82
Severity of dependence scale	4.00	13.00	8.73	2.23
MIDAS total score	7.00	270.00	69.60	49.18

Table 2 Follow-up dataset for continuous variables (paired samples statistics and *t* test)

	Baseline during withdrawal ($N = 20$)			1-year follow-up ($N = 20$)			*t* test
	Mean	SD	SE mean	Mean	SD	SE mean	Sig (two-tailed)
Frequency of attacks per month	22.15	6.42	1.44	11.60	7.32	1.64	0.00
Number of tablets per month	30.65	22.14	4.95	16.50	14.77	3.30	0.03
Pain intensity on VAS	7.85	1.46	0.33	6.60	1.76	0.39	0.01
HAM-A score	12.30	6.60	1.48	11.60	6.22	1.39	0.67
HAM-D score	12.00	6.52	1.46	9.10	5.46	1.22	0.03
Iowa gambling task net score	−7.70	17.32	3.87	−7.70	16.92	3.78	1.00
MIDAS total score	65.05	37.08	8.29	33.25	32.65	7.30	0.00

Discussion

The aim of this study was to show that migraineurs overusing painkillers, although forced to cope with chronic pain, often develop a behavioral addiction that might rise from the same decision-making deficit often described in substance abuse [11]. Moreover, follow-up at 12 months showed that, contrary to the global clinical and psychopathological improvement observed in these patients, decision-making was persistently impaired. Still, our data confirm the OFC hypometabolism described by Fumal et al. [14] in his PET study from a neuropsychological perspective. Taken together, this data show, in a preliminary but promising way, that even a non-psychotropic drug dependence can be associated with the fronto-striatal circuit impairment and decision-making deficit traditionally observed in different populations of addicts [8, 9, 11], and more recently also in people with binge eating disorder and pathological gambling. Thus, there is growing evidence in considering MOH part of the addiction spectrum [21].

After attesting to a persistent decision-making deficit in patients with MOH, yet recognizing the current small size of our follow-up sample, further studies are needed to elucidate the role of fronto-striatal circuit dysfunction. We believe that the impairment of fronto-striatal networks might constitute a psychobiological vulnerability [9] that, in this particular condition, influences the clinical onset of medication overuse and recurrent relapses in some patients with chronic migraine. Therefore, clinicians will hopefully use the IGT as a valid tool to identify chronic migraine patients at a higher risk for medication overuse and relapse, who might potentially require stricter monitoring.

Conflict of interest No current conflicts of interest for any of the authors.

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ORAL COMMUNICATIONS

Late-onset cluster headache: some considerations about 73 cases

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Abstract Data in the literature on cluster headache (CH) indicate a mean age at onset of about 29–30 years; recently, however, cases have been reported with onset in old age. A review of age at onset in all CH patients ($n = 693$) followed at the University of Parma Headache Centre between 1976 and 2011 shows that 73 (10.5 %) patients began to suffer from CH after age 50. In these 73 patient, the gender (M:F) ratio was 1.4:1, while in the 620 patients with CH onset before age 50, it was 2.5:1. In the patients with CH onset after and before age 50, respectively, the distribution by CH subtype shows that the episodic-to-chronic ratio was 7.6:1 and 7.9:1 in men and 1.5:1 and 7.8:1 in women. In episodic CH men with onset after 50 the average duration of active periods was 60 versus 39 days for those with onset before 50. In women, the duration was 80 and 42 days, respectively. In conclusion, our case review suggests that CH onset after age 50 is not rare, especially in women. Additionally, late onset represents a negative prognostic factor because, particularly in women, CH will more likely be a chronic form and even in episodic forms active periods will last longer.

Keywords Cluster headache · Epidemiology · Onset distribution by age · Onset distribution by gender

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Introduction

Cluster headache (CH) has always been considered a form of primary headache typically occurring in mid-adulthood. The broadest case series in the literature indicates a mean age at onset of about 30 years [1–4]. Recently, however, anecdotal cases [5–7] and small case series [4, 8, 9] have been reported that seem to suggest onset in old age, especially among women. As data on this subject are still scanty and conflicting, we thought it advisable to review our broad series of CH cases to evaluate: (a) the mean age at onset by gender and CH subtype (episodic and chronic); and (b) any clinical differences in CH patients related to age at onset.

Patients and methods

We considered all patients consecutively seen for the first time at the University of Parma Headache Centre between November 1975 and March 2011 who, based on their clinical records, met the following criteria: (a) diagnosis of episodic CH or chronic CH according to the International Classification of Headache Disorders, 2nd Edition (ICHD-II) of 2004 [10] (coded to 3.1.1 and 3.1.2, respectively); and (b) age at CH onset established with certainty.

In each of the 693 patients (487 men and 206 women) thus identified, we evaluated age and CH subtype at the time of the first visit, age at onset of CH, family history for headache in general and CH in particular, the presence or absence of head injury (with or without loss of consciousness) in the past medical history, smoking, alcohol and coffee intake, pain side during attacks, the patient's behaviour during attacks, the average number of attacks per day, the average duration of attacks and the average

duration of active periods in episodic CH. We also evaluated the presence of any autonomic signs and symptoms accompanying pain listed among the diagnostic criteria in the ICHD-II as well as the possible presence of nausea, vomiting, photophobia, phonophobia, and osmophobia.

The 693 CH patients were divided into two groups based on whether CH had set in before or after age 50. We then performed a comparative analysis of the personal and clinical features of patients between the two groups.

We chose the 50-year cut-off both because in our opinion it was suitable to distinguish between a "classic" and a "late" age at onset and because it allowed comparison with the few data existing in the literature on this subject [4, 9].

Data were processed using the Statistical Package for the Social Sciences (SPSS), version 17.

To assess the statistical significance of the differences between the two groups, we used the Chi-square test and Student's *t* test.

Results

Of the 693 patients studied, 606 had episodic CH and 87 chronic CH. The mean age at CH onset was 30.7 years (min. 3, max. 74—SD 13.8), and it was older in chronic (34.1 years) than in episodic forms (29.5 years) ($p < 0.01$).

Table 1 Distribution of the 693 CH patients by decade of age at onset and by gender

Age at onset (decades)	Episodic CH (M + F)	Chronic CH (M + F)	Total (M + F)
0–9 years	6 (4 + 2)	4 (1 + 3)	10 (5 + 5)
10–19 years	134 (85 + 49)	13 (6 + 7)	147 (91 + 56)
20–29 years	225 (159 + 66)	26 (21 + 5)	251 (180 + 71)
30–39 years	106 (81 + 25)	11 (9 + 2)	117 (90 + 27)
40–49 years	79 (65 + 14)	16 (13 + 3)	95 (78 + 17)
50–59 years	31 (23 + 8)	11 (3 + 8)	42 (26 + 16)
60–69 years	20 (12 + 8)	5 (2 + 3)	25 (14 + 11)
70–79 years	5 (3 + 2)	1 (0 + 1)	6 (3 + 3)
Total	606 (432 + 174)	87 (55 + 32)	693 (487 + 206)

The patients' distribution by decade of age at onset (Table 1) reveals CH onset between the second and the fourth decades of life in 74.3 % of cases. However, 73 patients (10.5 %, 43 men and 30 women) had CH onset after age 50, including 31 (17 men and 14 women) who first developed CH after 60.

Of the 73 patients with CH onset after 50, 56 had episodic CH and 17 chronic CH. Of the latter, as many as 12 were women and only 5 were men.

Of the 30 women with CH onset after age 50, 18 had episodic CH and 12 chronic CH. Of the 16 women with onset in sixth decade, episodic and chronic sufferers were eight each.

The comparison between the 73 CH patients with onset after 50 and the 620 CH patients with onset before 50 (Table 2) demonstrates a relatively higher rate of the chronic subtype in patients with onset at a later age (17/73 corresponding to 23.3 % vs. 70/620 corresponding to 11.3 %). This figure appears clearly determined by the higher proportion in women (12/30 corresponding to 40.0 % vs. 20/176 corresponding to 11.4 %). So in chronic CH, a remarkable difference emerged in the M:F ratio: this was 0.4:1 for chronic forms with onset after 50, meaning that it was reversed with respect to both episodic and chronic forms with onset before 50 (2.5:1) and also with respect to episodic forms with onset after 50 (2.1:1).

The average duration of active periods in episodic CH patients appears statistically significantly longer in patients with onset after 50 (69 vs. 40 days) especially in women (80 vs. 42 days).

No other statistically significant differences were found in CH clinical features and in the patients' lifestyle between the two groups with onset before or after 50.

Conclusions

Our data analysis reveals that CH onset in mature adulthood and old age is not rare and in any event it is more frequent than previously thought.

In agreement with what was reported by Ekbom et al. [4], our study shows that it occurs more frequently in

Table 2 CH onset before and after age 50: a comparison of patient distribution by gender and CH subtype

CH subtype	Onset <50 years		Onset >50 years		Total	
	(M + F)	M:F	(M + F)	M:F	(M + F)	M:F
Episodic	550		56		606	
	(394 + 156)	2.5:1	(38 + 18)	2.1:1	(432 + 174)	2.5:1
Chronic	70		17		87	
	(50 + 20)	2.5:1	(5 + 12)	0.4:1	(55 + 32)	1.7:1
Total	620		73		693	
	(444 + 176)	2.5:1	(43 + 30)	1.4:1	(487 + 206)	2.4:1

women who suffer from chronic CH. Additionally, if we consider that our episodic CH women with onset after 50 had significantly longer active periods than that with earlier onset, we can conclude that a late CH onset in women is an unfavourable prognostic factor.

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

The real usefulness and indication for migraine diagnosis of neurophysiologic evaluation

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Abstract According to IHS criteria, a correct clinical history is fully adequate for a diagnosis of migraine. Patients usually perform many useless instrumental and laboratoristic exams and specialistic evaluations. In particular, electroencephalogram (EEG) is often prescribed as a first-line study in migraine patients. The objective is to analyze the indications of EEG in migraine and to evaluate whether its performance may negatively influence the time necessary to obtain a correct diagnosis. In particular, we compared the effects of EEG performance with those related to neuroradiological examinations in terms of time necessary to obtain a migraine diagnosis. 400 consecutive patients affected by migraine without aura were enrolled. Demographic and clinical data were collected. We used an ordinal regression model considering diagnostic delay as the main outcome and EEG and radiological examinations (in particular brain CT) as predictors. Delay was defined as a time to diagnosis greater than 1-year. Age, sex, number of specialists and examinations were included in the model as covariates. EEG represented the most often performed non-radiologic examination in our sample (20 %). It was associated with a significant risk of diagnostic delay [OR 1.66 (95 % CI 1.65–1.66, $p < 0.001$)]. An appropriate workup, including CT scan and early referral to a headache center was the most time-saving approach, being associated to the lowest probability of diagnostic delay [OR 0.72 (95 % CI 0.63–0.82, $p < 0.001$)]. EEG is a frequently prescribed exam in migraine. Our data show that it can contribute to diagnostic delay, highlighting only uncertain and unspecific elements. These data confirm the usefulness of a wide application of IHS guidelines, not recommending this exam for migraine detection.

Keywords Migraine without aura · EEG · Diagnostic delay

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Introduction

Migraine without aura is one of the most diffuse pathological condition in the general population. Very often patients do not obtain a correct diagnosis and a consequent correct therapy for years. One possible reason for this can be related to the fact that general practitioners and specialists, including neurologists, usually recommend their patients to perform several instrumental exams. Electroencephalogram (EEG) is an easy and economic tool, useful in some neurological pathologies as for example in epilepsy diagnosis and follow-up. Moreover, it is a non-invasive exam, with a relatively short time necessary for the execution. For all these reasons, it is often prescribed as a first-line study in migraine patients.

2011 EFNS guidelines for the diagnosis of non-acute headache [1] report that an interictal EEG is not routinely indicated for headache diagnosis. The only indication regards the case of a differential diagnosis when a serious doubt of epileptic crisis exists. This kind of situation may especially emerge in migraine with atypical aura patients. However, migraine without aura attack presents typical, easy to identify features and IHS diagnostic criteria for

migraine diagnosis [2] represent an useful and simple tool to apply.

The aim of this study was to evaluate the real indications of EEG in migraine patients and to verify whether its performance was significantly related to an increase in the time necessary to obtain a correct diagnosis.

Methods

During a 2-year period, we considered all the consecutive patients referred to our headache center for a first diagnosis of migraine without aura and registered their demographic and clinical data. A final sample of 400 patients was selected. Exclusion criteria were (a) any headache different from migraine without aura; (b) presence of neurological co-pathologies; (c) incomplete clinical history. We paid particular attention to obtain information about time of symptoms' onset, the delay between migraine onset and the correct diagnosis, the number of different specialists consulted and the number and typology of radiologic, other instrumental and laboratoristic exams performed. We used an ordinal regression model considering delay as the main outcome and EEG and radiological examinations (in particular brain CT) as predictors. Delay was defined as a time from symptoms' onset to diagnosis greater than 1-year. Age, sex, number of specialists and examinations were included in the model as covariates. Data were analyzed in a full-factorial polytomous universal model. The main outcome and predictors thresholds were significant, indicating a substantial relationship between outcome and predictors ($p < 0.05$). Among the used covariates, patient's age and the total number of specialists consulted contributed significantly to the model ($p < 0.05$). Analysis was performed with SPSS 13.0 on Windows systems.

Results

Electroencephalogram was the most frequent non-radiologic examination performed in our sample, representing 20 % of the instrumental tests. It was associated with a significant risk of diagnostic delay [OR 1.66 (95 % CI 1.65–1.66, $p < 0.001$)], whereas the gold-standard examination, represented by a brain CT scan, was associated with a reduced probability of deferral [OR 0.72 (95 % CI 0.63–0.82, $p < 0.001$)] (Fig. 1). It was noticeable that the performance of no instrumental examination was associated to a slight increased risk of delay [OR 1.19 (95 % CI 1.10–1.29, $p < 0.001$)]. Increasing age and a high number of specialists consulted significantly contributed to the diagnostic delay in this model. An appropriate workup, including CT scan and early referral to a headache center was the most time-saving approach, being associated with the lowest probability of diagnostic delay.

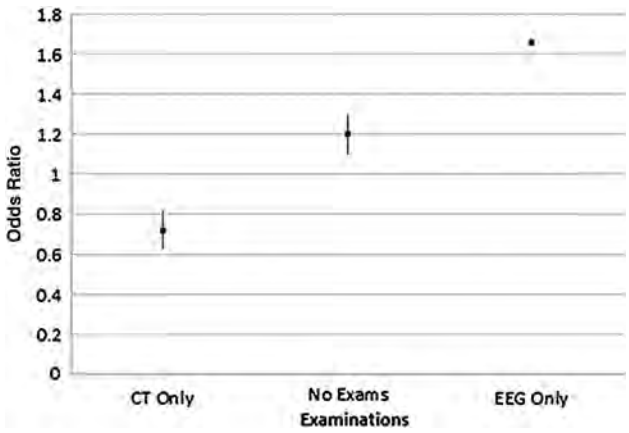

Fig. 1 Impact of EEG with respect to CT scan or no examinations on the risk of diagnostic delay

Discussion

Electroencephalogram was the most frequently performed instrumental exam in our patients, in spite of the lack of any indication in diagnostic guidelines where the correct diagnosis of migraine without aura is simply based on clinical information.

In the recent years, our research group demonstrated that a larger number of specialists consulted and a higher number of examinations performed can contribute to increase migraine diagnostic delay [3, 4]. Regarding EEG findings, very often migraineurs present EEG alterations like focal slow waves or sharp-waves [5]; these aspects, if evaluated by a non-neurologist specialist, can be considered as pathologic elements and can contribute to increase in diagnostic delay. In clinical practice, epileptic crisis are well differentiable from migraine without aura attack and the diagnosis of epileptic attacks should always be based on clinical considerations.

In conclusion, for the best management of migraine patients a specialistic evaluation in headache centers where an expert specialist can apply correct diagnostic criteria and prescribe appropriate instrumental examinations seems to be the most appropriate approach.

Conflicts of interest I certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

Detection of possible factors favouring the evolution of migraine without aura into chronic migraine

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Abstract In a minority of cases, the natural history of migraine without aura (MO) is characterised over time by its evolution into a form of chronic migraine (CM). In order to detect the possible factors predicting this negative evolution of MO, we searched in our Headache Centre files for all clinical records that met the following criteria: (a) first visit between 1976 and 1998; (b) diagnosis of MO or of common migraine at the first observation, with or without association with other primary headache types; (c) <15 days per month of migraine at the first observation; and (d) at least one follow-up visit at least 10 years after the first visit. The patients thus identified were then divided into two groups based on a favourable/steady evolution (Group A: $n = 243$, 195 women and 48 men) or an unfavourable evolution (Group B: $n = 72$, 62 women and 10 men) of their migraine over time. In the two groups, we compared various clinical parameters that were present at the first observation or emerged at the subsequent follow-up visits. The parameters that were statistically significantly more frequent in Group B—and can therefore be considered possible negative prognostic factors—were: (a) ≥10 days per month of migraine at the first observation; (b) presence of depression at the first visit in males; and (c) onset of depression or arterial hypertension after the first observation but before transformation to CM in females. Based on these findings, in MO patients the high frequency of migraine attacks, comorbidity with depression, and the tendency to develop arterial hypertension should require particular attention and careful management to prevent evolution into CM.

Keywords Migraine · Migraine without aura · Chronic migraine · Chronic daily headache · Chronic headache

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Introduction

Mean age at onset of migraine without aura (MO) is about 20 years. Onset may occur as early as in childhood, but very rarely does over 50. Around this age, most patients see that their migraine symptoms decrease and sometimes even resolve completely. In contrast, in a minority, but not negligible number, of patients, MO worsens over time, changing some of its previous clinical features and especially increasing in frequency until there are no more free intervals between attacks. Thus, MO is gradually transformed from a typical attack-like headache to a so-called chronic headache.

Several reports have been published on this subject in the literature. However, there is still no consensus of opinion on: (a) the type of headache that occurs in these patients; and (b) the factors that may favour MO worsening over time. We therefore tried to help clarify this issue by performing a review of the broad case series of patients followed over the years at our Headache Centre. We report here the preliminary data of our study. The final data will be presented in a future publication.

Patients and methods

We accessed the University of Parma Headache Centre files and took all clinical records of patients that met the

following requirements: (a) first visit between 1976 and 1998; (b) diagnosis of MO or of common migraine at the first observation, with or without association with other primary headache types; (c) <15 days per month of migraine at the first observation; and (d) at least one follow-up visit at least 10 years after the first visit.

The 348 patients (286 women and 62 men) thus identified were divided into groups based on the diagnoses made at the subsequent visits, and particularly the diagnosis made during the most recent visit at the Centre. Diagnoses were established according to the criteria of the International Classification of Headache Disorders, 2nd Edition (ICHD-II) of 2004 [1] and its 2006 revision (ICHD-IIR) [2].

The MO patterns that the 348 patients exhibited over the years varied widely, not only from patient to patient, but also within the same patient showing a course of alternating improvement and worsening. For that reason, in order to compare patients with a steady or favourable evolution of MO over time to patients with an unfavourable evolution, we excluded 33 patients (29 women and four men) who over the years showed a cyclically fluctuating migraine pattern or developed a new form of headache that might not necessary be interpreted as an evolution of their original MO.

The remaining 315 patients (257 women and 58 men) were divided into two groups based on a steady/favourable evolution (Group A: $n = 243$, 195 women and 48 men) or an unfavourable evolution (Group B: $n = 72$, 62 women and 10 men) of their migraine over time. In each of the two groups we compared not only the clinical features of MO that were originally present at the first visit, but also several parameters related to the patients' family, physiological, past, and recent medical histories, both at the first visit and at the subsequent follow-up visits. Statistical analysis was performed using Student's t test and the χ^2 test.

Results

Mean age at the first observation of the 315 patients included in the study was 32.0 ± 11.2 years, with no significant differences between the 257 women (32.1 ± 11.1 years) and the 58 men (31.6 ± 11.9 years). In the 72 patients with an unfavourable MO evolution, mean age at the first observation was older (Group B: 35.3 ± 11.6 years), though in a non-statistically significant way, than in the 243 patients with a steady/favourable evolution (Group A: 30.5 ± 11.1 years). The difference was more marked in men (38.7 ± 8.8 vs. 30.1 ± 11.8) than in women (34.8 ± 11.9 vs. 30.6 ± 10.9).

No statistically significant differences were found between Group A and Group B in age at the last observation (46.0 ± 11.5 and 52.2 ± 12.5, respectively), the number of years of observation (15.8 ± 4.4 and 15.0 ± 4.8), and the number of follow-up visits (3.8 ± 3.6 and 5.0 ± 4.8).

No significant differences were found between the two groups in age at onset of MO, family history of migraine, pain location, and duration of attacks at the time of the first observation.

If we exclude three patients in Group A (two women and one man) with a highly variable number of MO days per month and 12 patients—eight in Group A (seven women and one man) and four in Group B (three women and one man)—with no certain data in their clinical records about the number of MO days per month, the remaining 232 patients in Group A (186 women and 46 men) and the remaining 68 patients in Group B (59 women and nine men) showed a statistically significant difference in the number of MO days per month at the time of the first observation (Table 1).

In the patients' medical histories reported at the first observation, depression was more statistically significantly present ($p < 0.05$) in Group B men (6/9 corresponding to 66.7 %) than in Group A men (10/48 corresponding to 20.8 %).

Among the diseases that were reported at the subsequent visits but occurred before MO "chronification", Group B versus Group A women showed a statistically significantly higher rate of depression (27/62 corresponding to 43.5 % vs. 26/195 corresponding to 13.3 %, $p < 0.01$) and arterial hypertension (24/62 corresponding to 38.7 % vs. 35/195 corresponding to 17.9 %, $p < 0.01$).

No statistically significant differences were found between the two groups in the presence of other diseases (head injury, hypo- or hyper-thyroidism, colitis, allergy, insomnia, anxiety, and panic attack disorder), either at the time of the first observation or later.

Table 1 Number of days of migraine per month at the first visit

	≤5 days per month	6 to 10 days per month	11 to 15 days per month
Group A			
M	20 (41.7 %)	19 (39.6 %)	7 (14.6 %)
F	83 (42.6 %)	59 (30.3 %)	44 (22.6 %)
Total	103 (42.4 %)	78 (32.1 %)	51 (21.0 %)
Group B			
M	1 (10.0 %)	3 (30.0 %)	5 (50.0 %)
F	20 (32.3 %)	15 (24.2 %)	24 (38.7 %)
Total	21 (29.2 %)	18 (25.0 %)	29 (40.3 %)

11–15 days of MO per month versus ≤10 days of MO per month: Group A versus Group B: $p < 0.01$ for the total sample; $p < 0.05$ for both men and women

Conclusions

Our data analysis indicates that a high number of MO days per month, comorbidity with depression and susceptibility to arterial hypertension in women represent unfavourable prognostic factors for a possible "chronification" of MO. Therefore, it is extremely important that the presence of these elements in all MO subjects be investigated with the utmost care. If present, they should be managed in the most appropriate way in order to prevent migraine from turning chronic.

Conflict of interest None.

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ORAL COMMUNICATIONS

Disability and mood state in patients with episodic and chronic migraine associated to medication overuse

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Abstract This study aims to compare disability and mood state in patients with episodic (EM) and chronic migraine associated to medication overuse (CM-MO), and to assess the relationships between the two outcomes. Patients, matched for age and gender, were administered the MIDAS, the WHO-DAS-2 and BDI-2. Difference between EM and CM-MO was assessed with the Kolmogorov–Smirnov Test; difference in distribution of patients with severe disability and low mood was tested with contingency coefficient; the correlation between MIDAS, WHO-DAS-2 and BDI-2 was tested with Spearman's index. Seventy patients were enrolled: CM-MO patients reported higher BDI-2 scores and higher MIDAS and WHO-DAS-2 scores, and were more likely to have severe disability and low mood state than those with EM; BDI-2 scores were correlated with disability scores, particularly with WHO-DAS-2. The study shows that disability and mood state are negatively impacted by the presence of more frequent headaches and by the overuse of acute medications.

Keywords Disability · Depression · Migraine · World Health Organisation-Disability Assessment Schedule-2 · Beck Depression Inventory-2

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Introduction

The transition from episodic to chronic migraine, though not completely understood, may be influenced by lifestyle, life events, comorbid conditions and genetic terrain, and is mediated by medication overuse in predisposed subjects [1, 2]. Such a transition may determine increased disability [3] and may be accompanied by decreased mood state [4].

This study aims to compare disability and mood state in patients with episodic (EM) and chronic migraine associated to medication overuse (CM-MO), and to assess the relationships between the two outcomes.

Methods

In this observational cross-sectional study, age and gender-matched patients with EM (1.1 and 1.2 codes of the International Classification of Headache Disorders-2nd edition [5]) and with CM-MO according to Silberstein's criteria [6] were consecutively enrolled: EM were outpatients, while CM-MO were inpatients under detoxification treatment.

Disability was assessed with the Migraine Disability Assessment (MIDAS) [7] and the WHO Disability Assessment Schedule-2 (WHO-DAS-2) [8]; mood state with the Beck Depression Inventory-2 (BDI-2) [9].

Kolmogorov–Smirnov Test was used to assess differences between EM and CM for outcome variables. Patients were identified as having severe disability (MIDAS $\geq$21; WHO-DAS-2 >90° percentile) and low mood (BDI-2 >90° percentile): differences in distribution of patients with more severe disability and lower mood were tested using contingency coefficient. The correlation between BDI-2 total score, MIDAS and WHO-DAS-2 total score was tested with Spearman's index. $P < .05$ was used to set statistical significance.

Results

Seventy patients were enrolled. Basic demographic information and group differences are reported in Table 1. Compared to EM, CM patients reported significantly higher scores at MIDAS, at most of WHO-DAS-2 scales, as well as higher Somatic-Affective and Total BDI-2 scores.

Table 2 shows the results of contingency coefficient: CM patients were more likely to have severe disability and lower mood state than those with EM.

BDI-2 correlated better with WHO-DAS-2 (RHO = 0.53, $P < .001$) than with MIDAS (RHO = 0.38, $P = .001$).

Discussion

This study shows that patients with CM-MO report worse disability and lower mood state and that they are more likely to have severe disability and low mood state compared to those with EM. Depression was strongly

Table 2 Cross-tabulation: health condition in relationship with disability and mood state severity groups

	EM	CM-MO
MIDAS		
≤20	19	5
≥21	16	30
Contingency coefficient = 0.388; $P < .001$		
WHO-DAS-2 global score		
<90° percentile	34	29
>90° percentile	1	6
Contingency coefficient = 0.232; $P = .046$		
BDI-2 Total score		
<90° percentile	31	20
> 90° percentile	4	15
Contingency coefficient= 0.333; $P = .003$		

EM episodic migraine, *CM-MO* chronic migraine associated to medication overuse, *MIDAS* Migraine Disability Assessment, *WHO-DAS-2* World Health Organization Disability Assessment Schedule, *BDI-2* Beck Depression Inventory

Table 1 Sociodemographic information and Kolmogorov–Smirnov test between EM and CM-MO patients

	EM	CM-MO	*P*
Age (mean ± SD)	42.8 ± 10.7	42.7 ± 10.2	.98
Gender (no.)			
Females	30	30	
Males	5	5	
Education (no.)			
Up to secondary school	13	14	
High school	14	10	
Academic	8	11	
Occupation (no.)			
Employed	24	29	
Student	2	–	
Not employed	4	3	
Not employed (health reasons)	–	1	
Retired	5	2	
MIDAS (mean ± SD)	24.4 ± 24.3	74.5 ± 64.6	<.001
WHO-DAS-2 (mean ± SD)			
Understanding and Communicating	10.9 ± 14.3	26.7 ± 18.6	.001
Getting around	13.7 ± 18.3	20.4 ± 20.4	.486
Self-care	2.9 ± 6.7	8.3 ± 11.9	.320
Getting along with people	8.7 ± 13.4	19.2 ± 19.5	.033
Daily activities–household	26.0 ± 24.4	35.7 ± 28.4	.683
Daily activities–work/school	19.8 ± 21.3	32.3 ± 18.0	.001
Participation in society	18.1 ± 14.8	35.7 ± 15.5	<.001
Global disability score	14.6 ± 11.5	26.6 ± 12.5	<.001
BDI-2 (mean ± SD)			
Somatic-Affective score	5.8 ± 4.1	10.8 ± 5.4	.007
Cognitive score	3.2 ± 3.5	5.7 ± 4.6	.115
Total score	9.1 ± 7.0	16.5 ± 8.8	.007

EM episodic migraine, *CM-MO* chronic migraine associated to medication overuse, *MIDAS* Migraine Disability Assessment, *WHO-DAS-2* World Health Organization Disability Assessment Schedule, *BDI-2* Beck Depression Inventory

correlated to disability, in particular when measured with the WHO-DAS-2. Previous studies showed that patients with CM-MO display higher disability and lower mood compared to EM [3, 4], but mood state has never been connected to disability, measured with a multi-domain assessment tool like the WHO-DAS-2.

Although the study is limited by a small sample size, it shows that ability to function and mood state may be negatively impacted by more frequent headaches and by the overuse of acute medications. As also previously reported [10, 11], the joint utilisation of migraine-specific and generic disability measures provides complementary information which enables comparison between different health conditions and makes it possible to evaluate patients' state according to a broad perspective, which in turns impacts on medical, social and health aspects of patients' lives.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

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ORAL COMMUNICATIONS

Stroke risk and migraine: near-infrared spectroscopy study

S. Viola · P. Viola · P. Litterio · M. P. Buongarzone · L. Fiorelli

Abstract Migraine has been associated with an increased risk for ischemic stroke. A recent study suggests that a generalized peripheral vasoconstriction may represent one possible mechanism underlying the increased risk for ischemic stroke. The aim is to verify the presence of cerebral arteriolar vasoconstriction during the interictal period of migraine with (MA+) and without aura (MA−). We studied 10 patients with MA+ (age 39.5 ± 12.2 years), 10 with MA− (age 40.3 ± 10.2 years), according to ICHD-II criteria 2004, during the interictal period of migraine, and 15 age- and sex-matched healthy control subjects. At rest in all the participants, the time-delay in millisecond (ms), between the R-wave of an electrocardiogram and the arterial pulse wave of cerebral microcirculation detected by transcranial near-infrared spectroscopy (R-APWCMtd) on the frontal cortex of both side, was determined to evaluate the presence of cerebral arteriolar vasoconstriction. The patients with migraine had a significantly longer R-APWCMtd than the control subjects: the patients with MA+: +38.3 ms, $p < 0.0002$; the patients with MA−: +34.7 ms, $p < 0.0002$. Our study seems to indicate that the migraine is independently associated with a mild vasoconstriction of cerebral arterioles that may represent one possible mechanism underlying the increased stroke risk especially in patients with MA+.

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Keywords Stroke risk · Migraine · Near-infrared spectroscopy

Introduction

Migraine, a common chronic disorder affecting up to 14 % of the general population, is a risk factor for ischemic stroke and other cardiovascular events (CVE), including angina pectoris, coronary artery vasospasm and myocardial infarction, especially in the subgroup with aura (MA+) [1]. The relative risk (RR) of ischemic stroke is increased in people with migraine with MA+ (RR 2.27) and migraine without aura (MA−) (RR 1.83) [2]. The mechanisms that link migraine to these vascular diseases remain uncertain. During the interictal phase of migraine, a recent study shows that both the large artery stiffness and pulse wave reflection are increased in patients with migraine, particularly MA+, suggesting the presence of a generalized peripheral vasoconstriction [1]. In this study, the author concludes that the migraine is independently associated with generalized peripheral vasoconstriction that may represent one possible mechanism underlying the increased risk for CVE and ischemic stroke.

The aim of our study is to verify the presence of cerebral arteriolar vasoconstriction during the interictal period of migraine with MA+ and MA−.

Methods

The patients with migraine were consecutively recruited at the outpatient Headache Center of the Neuroscience Department of our hospital from December 2010 to November 2011. The study was approved by the local

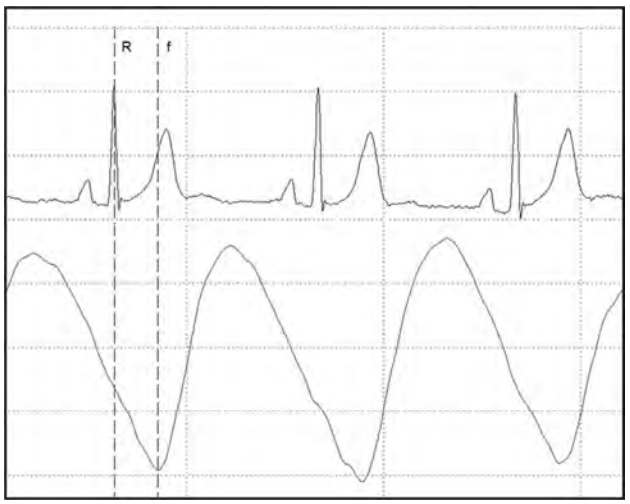

Fig. 1 The time-delay (218 ms) between the R-wave of an electrocardiogram and the foot (f) of arterial pulse wave of cerebral microcirculation (R-APWCMtd) detected by transcranial near-infrared spectroscopy in a control subject on F2 area

ethics committee. All the patients and control subjects gave their informed consent prior to inclusion in the study.

We studied 10 patients with MA+ (age 39.5 ± 12.2 years), 10 with MA− (age 40.3 ± 10.2 years), according to ICHD-II criteria 2004, during the interictal period of migraine, and 15 age- and sex-matched healthy control subjects. We excluded secondary headaches by appropriate laboratory and imaging diagnostic tests. The cases and controls were free from overt CVE, transient ischemic attack (TIA), ischemic stroke, major cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia) and migraine prophylactic medications. Subjects were asked not to use any inflammatory or analgesic drugs for 3 day before examination. At rest in all the participants, the time-delay in millisecond (ms) between the R-wave of an electrocardiogram and the foot of arterial pulse wave of cerebral microcirculation (R-APWCMtd), detected by transcranial near-infrared spectroscopy (T-NIRS Evolution II, CW system 760–850 nm) on the frontal cortex of both side (position F1, F2 of the international 10–20 EEG system), was determined (Fig. 1). Blood pressure was measured on the left arm in the patients and controls.
Statistical analysis: the data were analyzed using *t* test.

Results

The patients with migraine had a significantly longer R-APWCMtd than the control subjects: the patients with MA+: +38.3 ms, $p < 0.0002$; the patients with MA−: +34.7 ms, $p < 0.0002$. There was no significant difference between the right and left R-APWCMtd of frontal cortex in the migraine patients $p = 0.77$ and controls $p = 0.70$. There was no significant difference in the brachial blood pressure values between the patients and controls $p = 0.75$.

Discussion

Every heartbeat causes a pulsatile pressure gradient that propagates through the arterial network (aorta, carotid arteries, cerebral microcirculation that includes arterioles, capillaries and venules) and causes local changes in blood flow and volume. The local changes in blood volume are due to the elastic wall of the arterial network. In the microcirculation of cerebral cortex, small local changes in blood volume are still present and are revealed by means of NIRS that we call arterial pulse waves of cerebral microcirculation (APWCM). This longer R-APWCMtd suggests a mild vasoconstriction of cerebral arterioles in our migraine patients, especially in the patients with MA+: we suppose that the pulsatile pressure gradient propagates more slowly in presence of an increased intensity of pulse wave reflection due to a vasoconstriction of cerebral arterioles (resistance vessels). To confirm our theory, we can perform a simple test: it is known that hypercapnia and hypocapnia induce cerebral vasodilation and vasoconstriction, respectively. Inducing hypercapnia and hypocapnia in our controls, by means of breath-holding for 30 s and hyperventilation for 1 min, respectively, we measure a significantly shorter and longer R-APWCMtd, respectively, compared to rest (our unpublished data). In our study, we excluded all subjects with major vascular risk factors, CVE, TIA or ischemic stroke and migraine prophylactic medications. The patients and controls were matched by age and sex and the subjects were asked not to use any inflammatory or analgesic drugs for 3 days before examination; all conditions that may chance the resistance of cerebral arterioles and thus R-APWCMtd.

Migraine is associated with a higher risk for ischemic stroke and CVE, which cannot be explained exclusively by established cardiovascular risk factors [1].

From the literature, several potential mechanisms can be hypothesized. One possible mechanism is that the vasoconstriction of cerebral arterioles, that we find in our migraine patients during the interictal phase, especially in the patients with MA+, may reflect the presence of an endothelial dysfunction. The endothelial dysfunction is characterized by reduction in bioavailability of vasodilator (such as nitric oxide), increase in endothelial-derived contracting factors, and thus by a presence of vasoconstriction. It also comprises endothelial activation, characterized by a procoagulant, proinflammatory and proliferative action, which, in turns, predisposes to an increased rate of vascular ischemic events [3].

In conclusion, our study seems to indicate that the migraine is independently associated with a mild vasoconstriction of cerebral arterioles that may represent one possible mechanism underlying the increased stroke risk, especially in patients with MA+. The present findings seem to be consistent with other research [1, 4].

The measure of R-APWCMtd by means of NIRS and an electrocardiogram may represent a simple and non-invasive method to evaluate the vasoconstriction of cerebral microcirculation. Finally, the sample size was relatively small, and further confirmation by a study with a larger population is needed.

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

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ORAL COMMUNICATIONS

Implementing gnathological and neuromuscular concepts in patients with chronic migraine

H. Didier · C. Marchetti · A. Marchetti · D. D'Amico · V. Tullo · G. Bussone · F. Santoro

Abstract Temporomandibular disorders are among the potential comorbidities of migraine, and recent reports showed that they may have a role in promoting its progression into chronic migraine (CM). In order to clarify the possible role of neuromuscular components of the stomatognathic system in patients with CM, we studied 18 patients admitted as inpatients at our Headache Unit to undergo a withdrawal protocol for medication overuse, who underwent orthosis, after clinical and instrumental gnathological evaluation. They were subsequently evaluated after 6 months. The values of electromyographic parameters as well as of pain outcomes showed a significant decrease after orthosis. The implementation of gnathological and neuromuscular concepts can have a relevant role in the management of CM patients, in the contest of a multidisciplinary approach.

Keywords Chronic migraine (CM) · Gnathological evaluation · Orthosis · TENS

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Introduction

It is known that temporomandibular disorders (TMD) may cause headaches or worsen concurrent primary headaches, mainly tension-type headaches [1]. Recent reports have suggested that TMD are very common also in patients with migraine [2], and that they may have a role in migraine progression into chronic migraine (CM) [3]. CM patients, particularly those in whom medication overuse (MO) is present, are often difficult to treat, and require a multidisciplinary approach, particularly for the presence of possible comorbidities or concurrent conditions which may contribute to the progression to CM and/or to refractoriness to pharmacological therapy [4, 5].

Withdrawal of overused medication is generally recommended in CM with MO patients [6, 7] and it is in fact the preferred approach in our Headache Unit, in which inpatient withdrawal therapy is performed for CM patients with a long history of MO and with comorbidities [6]. In the context of this strategy, gnathological assessment is performed in those patients with suspected abnormalities in the neuromuscular component of the cranio-mandibular area.

The importance of neuromuscular factors rather than anatomical aspects in the origin of TMD has lead to the development of specific clinical and instrumental evaluations, which can be taken into account to produce a removable mandibular orthotic application. Orthosis (Fig. 1) is a mobile device to be worn continuously by the patient in order to facilitate stabilization of the mandible as well as physiological functioning of masticatory muscles [8].

Our purpose was to clarify the possible role of neuromuscular components of the stomatognathic system in patients with CM and MO.

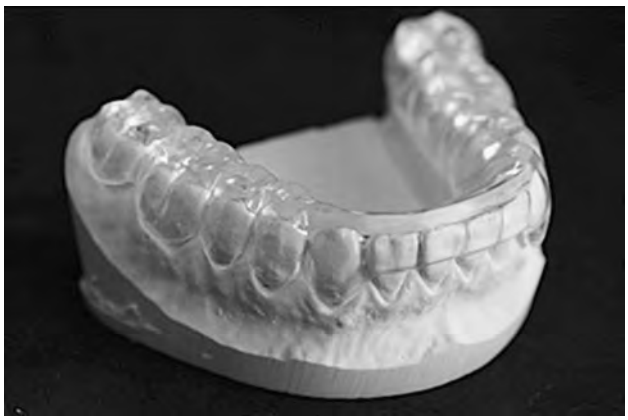

Fig. 1 Removable mandibular orthotic appliance

Materials and methods

Twenty-seven consecutive patients with CM (7 men and 20 women) admitted as inpatients at the Headache Unit of the Neurological Institute Carlo Besta to undergo a withdrawal protocol were enrolled. All of them fulfilled diagnostic criteria for CM with MO [9]. After 1 week of drug withdrawal, they underwent a specific clinical and instrumental gnathological check-up, including pain evaluation by VAS, detection of parafunctional activities, exclusion of inflammatory processes through objective evaluation and X-ray examination. Patients were subsequently evaluated under electromyography and kinesiography to identify the physiological rest position of the mandible after the masticatory muscle deprogramming obtained by TENS. The kinesiographic and electromyographic (CMS-EMG) evaluation is a computerized examination, designed by Bernard Jankelson to study mandibular kinematics and muscle activity and to record the physiological mandibular trajectory, thanks to TENS stimulation [10]. It is a painless and non invasive instrumental examination. The instrumentation used (Myotronics/Normed Inc. Tukwila, Washington) consists of a K7/EMG electromyograph, a K7/CMS kinesiograph with its magnet (Fig. 2) and a J4 myomonitor TENS (Fig. 3) unit with Myotrode SG mono-polar electrodes. EMG values were recorded for the right and left masseter muscles and anterior temporalis muscles.

Acquisition of data was performed in each patient according to the following protocol: EMG values in habitual mandibular rest position; EMG values after 45 min of TENS relaxation to check that muscle relaxation occurred; recording of both the rest position and neuromuscular trajectory induced by TENS, with subsequent comparison with the usual open-close trajectory, measurement of any discrepancy concerning the antero-posterior and latero-lateral planes, with ideal trajectories corresponding both sagittally and frontally; making of neuromuscular orthosis.

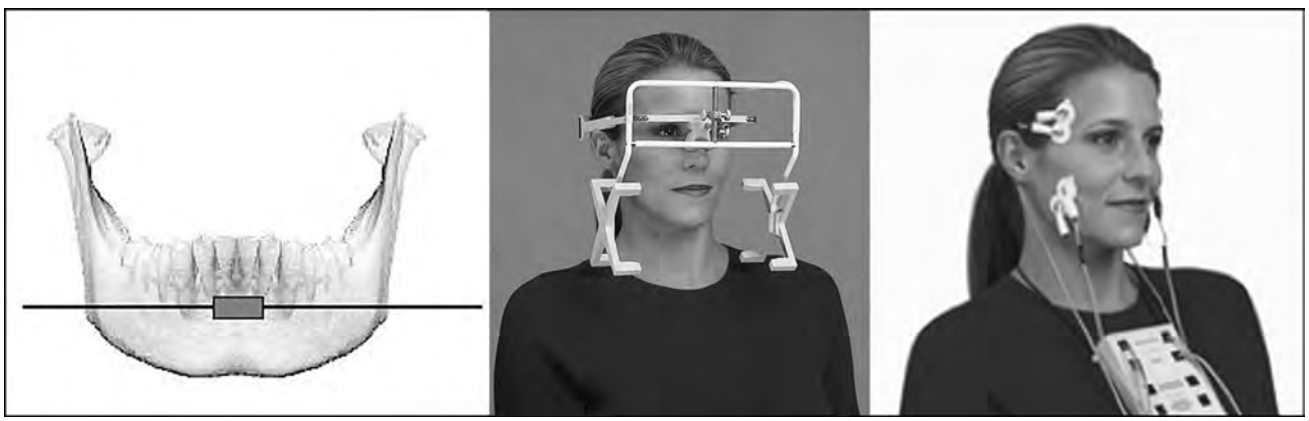

Fig. 2 K7/EMG electromyograph, K7/CMS kinesiograph with its magnet

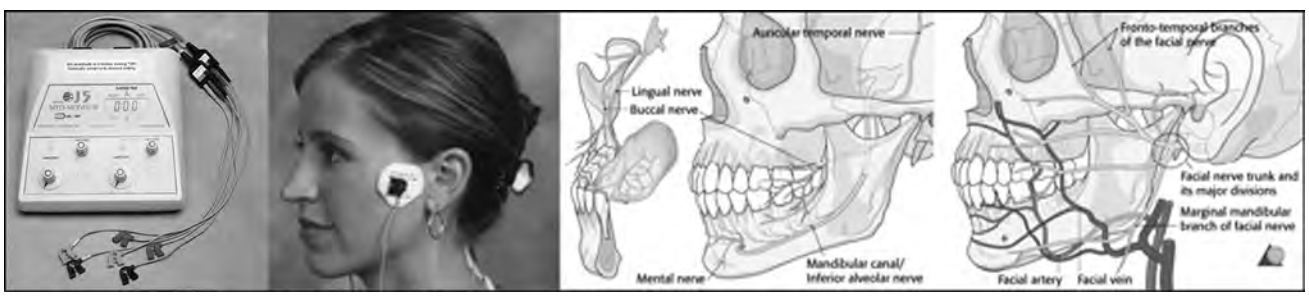

Fig. 3 J4 myomonitor TENS

According to our experience [11], clinical improvement in headache parameters after orthosis is likely to occur in those subjects presenting with a lateral deviation higher than 0.4 mm (Fig. 4), and reporting at least five parafunctional activities. For these reason, we will report the data obtained in those patients fulfilling these requirements.

All the enrolled patients followed a treatment plan with prescription of pharmacological prophylaxis with antimigraine drugs and/or antidepressants, after the patient withdrawal protocol of 8–10 days, and returned at follow-up visit after 6 months, which included clinical and instrumental gnathological re-evaluation, similar to the initial evaluation.

The differences in clinical and instrumental data between the initial evaluation and the follow-up visit were evaluated. Statistical analysis was performed using paired *t* test.

Results

Eighteen patients out of the initial sample of 27 were considered as candidates for orthosis after the initial clinical and instrumental evaluations. All patients returned to the 6-month follow-up visit. They were 6 men and 12 women; their mean age was 36.8, SD 13.2 years, and the mean history of CM at enrolment was 7.2, SD 7.2 years. The mean value of mandibular deviation at the first evaluation was 0.7 mm, SD 0.4.

When data recorded at the time of the first examination were compared to those recorded at the follow-up visit, significant improvements were observed after 6 months from application of orthosis.

The values of electromyographic parameters decreased from the initial evaluation to the 6-month follow-up, with significant differences. Detailed results are reported in Table 1.

Improvement in pain outcomes was also evident. The mean VAS values decreased from 5.4, SD 1.6 at the initial evaluation to 3.1, SD 1.6 at follow-up, the mean difference being −2.36, 95 % CI (−2.93 to −1.80). The mean pain score decreased from 8.8, SD 0.8–6.7, SD 1.3, the mean difference being −2.14, 95 % CI (−2.7 to −1.6). Differences were significant, with $p < 0.0001$ for both parameters.

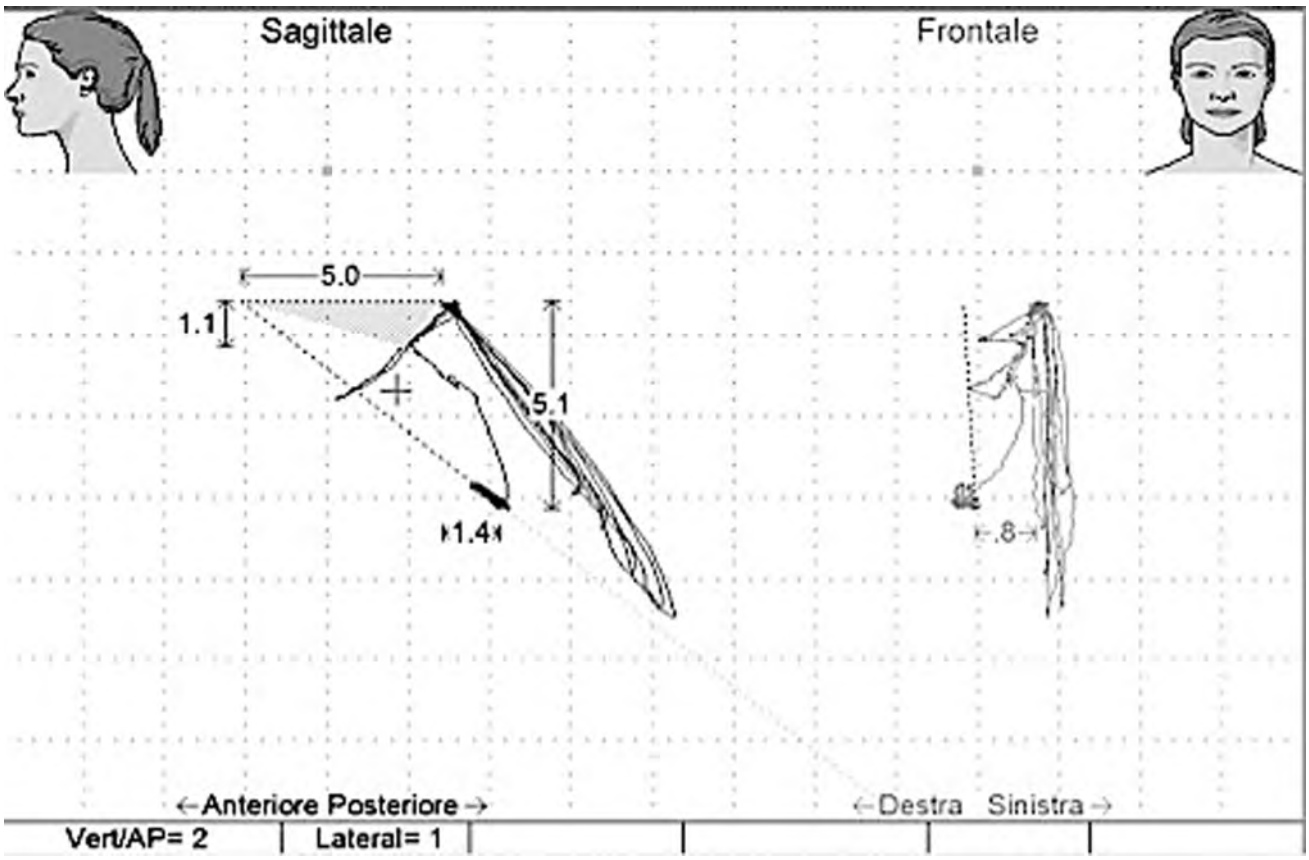

Fig. 4 Neuromuscular trajectory compared to habitual trajectory: we can measure 5 mm of advancement (Sagittal plane) and 0.8 of lateral deviation (frontal plane)

Table 1 Electromyographic parameters in a sample of CM patients: comparison of values at the initial evaluation and at to the 6-month follow-up

MUSCLE	R-side before orthosis	R-side after orthosis	Mean difference	*P* value	L-side before orthosis	L-side after orthosis	Mean difference	*P* value
Anterior temporalis	3.6 microV SD 1.8	1.7 microV SD 0.7	−1.9 microV 95 % CI (−2.8 to −1.0)	<0.0003	3.6 microV SD 1.5	1.8 microV SD 0.7	−1.8 microV 95 % CI (−2.6 to −1.1)	<0.0001
Masseter	3.1 microV SD 2.0	1.3 microV SD 0.5	−1.8 microV 95 % CI (−2.7 to−0.8)	<0.0010	3.5 microV SD 2.0	1.4 microV SD 0.4	−2.2 microV 95 % CI (−3.1 to −1.3)	<0.0001

Statistical analysis by paired *t* test

Discussion and concluding remarks

Although often not recognized, TMD are among the potential comorbidities of migraine, and may have a role in promoting and maintaining migraine progression into a more disabling and difficult to treat form, i.e. chronic migraine (CM) [2, 3].

The results of the present study confirm that muscular alterations in the stomatognathic system may be the highly prevalent among patients with CM. They also show an improvement in headache parameters after orthosis application. Although the design of the study does not allow to calculate the specific effect of this intervention (as patients were followed in a comprehensive treatment plan which included pharmacological treatments), the fact that clinical outcomes were paralleled by evident changes in neuromuscular instrumental findings suggests the efficacy of orthosis in the management of CM.

These findings are in line with the results of several lines of research, showing that neuromuscular orthosis can largely contribute to relieve headache symptoms [8] and that TENS is able to promote relaxation of masticatory muscles, reducing their mechanical and metabolic stress, and also inducing endorphin and cortisol release [12].

It is important to note that TMD and cutaneous allodynia are associated in individuals with migraine as in fact central sensitization, and cutaneous allodynia—which is its clinical surrogate—are among the most relevant risk factor for migraine progression and for development of CM [13]. In conclusion, we think that the implementation of gnathological muscular concepts can have a relevant role in the management of headache patients, particularly in the contest of a multidisciplinary approach to patients suffering from such a disabling form as CM.

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

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ORAL COMMUNICATIONS

SPARTACUS: underdiagnosis of chronic daily headache in primary care

G. Giannini · V. Favoni · S. Bauleo · T. Ferrante · G. Pierangeli · F. Albani · M. L. Bacchi Reggiani · A. Baruzzi · P. Cortelli · S. Cevoli

Abstract Despite the burden of chronic daily headache (CDH), general practitioners' (GPs) ability to recognize it is unknown. This work is a sub-study of a population-based study investigating GPs' knowledge on their CDH patients. Patients diagnosed with CDH through the screening questionnaire were interviewed by their GPs who indicated if subjects were known as patients suffering from CDH with medication overuse (MO), CDH without MO, episodic headache (EH) or non-headache sufferers. Our study showed that 64.37 % of CDH sufferers are misdiagnosed by their GPs. However, overusers are better known to GPs.

Keywords Underdiagnosis · General practitioners · Migraine · Chronic daily headache

Introduction

Despite its heavy burden, migraine is underdiagnosed and unrecognised both in Europe and USA [1, 2]. This is a hurdle in providing migraineurs with appropriate treatment and management. A significant amount of attention should be given to CDH as it is more disabling, has a higher impact on work than episodic migraine and requires great access to health care services [3]. Some studies based on self-reported questionnaires showed that an important rate of CDH sufferers has never consulted doctors for their headache [2, 4, 5]. Nevertheless, direct information from GPs about it is largely lacking. Many studies pointed out that headache sufferers receive a sub-optimal medical approach and also that acute headache medication is frequently overused while prophylactic medication is rarely used by CDH patients [1, 2, 5]. As far as we know, this is the first study that investigates GPs' knowledge on their CDH patients.

Method

The present work is a sub-study of a population-based, observational, cross-sectional study. We sent an ad hoc validated questionnaire (sensitivity 97 %, specificity 86 %) to 25,163 adult subjects registered in the lists of 20 GPs in the Casalecchio di Reno district, which includes rural and urban zones. The study population was therefore representative of the general population in Emilia–Romagna Region (Northern Italy). CDH was defined as headache occurring at least 15 days per month for at least 3 months and MO was defined using the ICHD-2R criteria [6]. A self-addressed stamped envelope was enclosed to return the survey. Patients resulting positive were interviewed by

S. Bauleo is the member of General Practitioner's study group, AUSL of Bologna.

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their GPs through a semi-structured questionnaire. GPs indicated if subjects were known as patients suffering from CDH with MO, CDH without MO, EH or non-headache sufferers. Patients whose questionnaires were incomplete were contacted by phone by researchers to improve the study's sensibility. GPs were then asked about their knowledge of these patients. Chi-squared were performed to compare the GPs' knowledge between groups. Significance level was set at $p \leq 0.05$.

Results

16,577 subjects returned the completed questionnaire (65.88 %), 636 (3.84 %) of which were affected from CDH: 239 of those (1.44 %) with MO and 397 (2.40 %) without MO. CDH patients' complete questionnaires were 435/636 (127 with MO: 31 male and 96 female; 308 without MO: 64 male and 244 female). 62 (48.82 %) subjects suffering from CDH with MO were already known as such to GPs while 13 (10.24 %) were known as CDH without MO, 31 (24.41 %) as affected from EH and 21 (16.54 %) as non-headache sufferers. In the CDH without MO group 93 (30.19 %) patients were known as such, 97 (31.49 %) as EH, 104 (33.77 %) as non-headache sufferers and 14 (4.55 %) as medication overusers. Globally, only 155 (35.63 %) of CDH sufferers are still known as such by their GPs while 280 (64.37 %) are misdiagnosed. In both CDH groups, comparing correctly diagnosed and misdiagnosed subjects by their GPs, we have highlighted that overusers are better known to GPs [62 (48.82 %) vs. 93 (30.19 %) $p < 0.001$]. This statistical significance is attributable to women [50 (52.08 %) vs. 78 (31.97 %) $p < 0.001$] and not to men [12 (38.71 %) vs. 15 (23.44 %) $p = 0.192$] (Tables 1, 2).

Conclusions

Our study stresses that 64.37 % of CDH sufferers are misdiagnosed by their GPs. For its impact on public health, this kind of chronic pain should therefore get more attention. The reasons of this lack of knowledge are unknown: patients probably manage their headache on their own, recurring to aspecific medications, and do not feel the need for further help, or CDH may represent for them just a minor problem in a co-morbidity of other pain conditions as reported in some studies [2, 4, 5, 7]. Other studies highlighted another reason to it: migraineurs not consulting their GPs are patients who believe that consultation would not do them much good [7]. 28.7 % patients, 16.5 % of which with MO and 33.8 % without MO, were known as

Table 1 GPs knowledge of their CDH patients

Patients	Known to GPs	Total	%	Male	%	Female	%
CDH with MO	Known as CDH with MO	62	48.82	12	38.71	50	52.08
	Known as CDH without MO	13	10.24	4	12.90	9	9.38
	Known as EH	31	24.41	8	25.81	23	23.96
	Known as non-headache sufferers	21	16.54	7	22.58	14	14.58
		127		31		96	
CDH without MO	Known as CDH with MO	14	4.55	2	3.13	12	4.92
	Known as CDH without MO	93	30.19	15	23.44	78	31.97
	Known as EH	97	31.49	22	34.38	75	30.74
	Known as non-headache sufferers	104	33.77	25	39.06	79	32.38
		308		64		244	

CDH Chronic daily headache, *MO* medication overuse, *EH* episodic headache, *GPs* general practitioners

Table 2 Chi-square comparing correctly diagnosed and misdiagnosed subjects by their GPs

	Sufferers from CDH with MO correctly diagnosed (%)/ misdiagnosed (%)	Sufferers from CDH without MO correctly diagnosed (%)/ misdiagnosed (%)	*p* value
Total	62 (48.82)/65 (51.18)	93 (30.19)/215 (69.81)	<0.001
Male	12 (38.71)/19 (61.29)	15 (23.44)/49 (76.56)	0.192
Female	50 (52.08)/46 (47.92)	78 (31.97)/166 (68.03)	<0.001

CDH Chronic daily headache, *MO* medication overuse

non-headache sufferers: we can speculate that they probably never consulted their GP for headache. These results are higher than those of the Akershus study showing that 20 % of CDH sufferers (17 % with MO and 22 % without MO) never consulted their GPs [5]. However, there are strong methodological differences with our study: the Akershus study results were obtained retrospectively by clinically interviewing CDH patients who self-reported the prior level of contact due to headache, whereas our results were obtained directly by GPs. Moreover, the Akershus study considers only persons aged 30–44 and focuses only on primary CDH. Although insufficient, patients with CDH with MO are better diagnosed than those without it. A possible explanation is that overusers need medical prescriptions. These results suggest that a cooperative network involving GPs, neurologists and headache specialists is strongly recommended to advance medical education and improve CDH diagnosis and management.

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

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ORAL COMMUNICATIONS

Headache at high school: clinical characteristics and impact

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Abstract Although migraine (MH) and tension type headache (TTH) are the most common and important causes of recurrent headache in adolescents, they are poorly understood and not recognized by parents and teachers, delaying the first physician evaluation for correct diagnosis and management. The purpose of this study is to assess the knowledge about headache impact among the students of a Communication Private High School in Rimini city, and to evaluate the main different types of headaches interfering with school and social day activities. A self-administered questionnaire interview was given to students of the last 2 years of high school; ten items assessed the headache experience during the prior 12 months, especially during school time: the features and diagnosis of headaches types (based on the 2004 IHS criteria), precipitating factors, disability measured using the migraine disability assessment (MIDAS); therapeutic intervention. Out of the 60 students, 84 % experienced recurrent headache during the last 12 months. 79 % were females, aged 17–20 years; a family history was present in 74 % of headache students, in the maternal line; 45 % of subjects were identified as having MH and 27 % TTH; 25 % had morning headache and 20 % in the afternoon; fatigue, emotional stress and lack of sleep were the main trigger factors for headache, respectively in 86, 50 and 50 % of students; 92 % of headache students could not follow the lessons, could not participate in exercises and physical activity because of the headache; none had consulted a medical doctor and the 90 % of all students had never read, listened or watched television about headache. This study remarks on the need to promote headache educational programs, starting from high school, to increase communication between teachers–family–physician and patient-adolescents, with the goal to have an early appropriate therapeutic intervention, improvement of the quality of life and to prevent long-term headache disease in the adult age.

Keywords Migraine · Tension type headache · Impact · Adolescents · High school

Introduction

Headaches are very frequent in adolescence, especially migraine headache (MH) and tension type headache (TTH), whose prevalence is respectively, 8–10 and 15–20 % [1–6]. They can be seriously disabling, interfering with various aspects of everyday life, not just in the family but particularly at school and in inter-person relations [7]. MH is more likely to be associated with stressful experiences such as excessive school demands, school overload, social isolation, perceived teacher unfairness or, later, job dissatisfaction [8, 9]. Even so, relatives and teachers often fail to understand headache and underrate it, and delay sending the sufferer to consult a doctor for appropriate treatment, preferring self-medication.

The aim of this study was to assess the impact of headache among high school students and examine the

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main types of headaches that interfere with school and daytime social activities.

Materials and methods

Students in the two senior classes at the Communication Private High School "Maestre Pie" in Rimini (Italy) were invited to take part in a study to assess their experience of headaches during the previous 12 months, especially during school time. A self-administered questionnaire interview was done during school hours, consisting of ten items which reported basic personal details and family history; diagnosis of headache based on three typical headache features (according to the 2004 IHS diagnostic criteria), one for MH, one for TTH and one for unclassifiable headache; at what time of day the headache started, triggering factors; disability measured using the migraine disability assessment (MIDAS); and treatment. Descriptive statistical analysis was done.

Results

A total of 60 students aged 17–20 years, 79 % females, were analyzed; 84 % (51) reported recurrent headache during the last 12 months; 25 % had headache during morning lessons, 20 % in the afternoon and only 3 % in the evening; 52 % did not specify. A family history was reported by 74 % of the sufferers, in the maternal line. Nearly half, 53 % (27 subjects), were identified as having MH and 31 % (16) TTH; the remaining 16 % (8) had unclassifiable headaches. In 37 % of the MH sufferers the headache lasted from 6 to 72 h; it was strong in 36 %; pulsating in 43 %, and got worse with movement (gym, jogging, going up stairs) in 57 %. A quarter (25 %) felt nauseous during the attack and 7 % vomited. Just over half (52 %) reported photophobia and 72 % phonophobia; 43 % did not eat during their break or at lunch.

Among those who reported TTH, 30 % had pain throughout the head; 30 % said it was mild and 44 % moderate.

Table 1 lists the main causes of the headaches. The most frequent triggers were tiredness, stress in general or in relation to some task or tests during a lesson, and too little sleep.

The MIDAS questionnaire was completed by 45 headache students. Of these, 62 % (28) rated their disability as grade I, minimal or infrequent (mean score 1.64); 17 % (8) rated it as grade II, mild or infrequent (mean score 8.37); 11 % (5) opted for grade III, moderate (mean score 14.2) and 9 % (4) for grade IV, severe (mean score 51.25). Most of the headache sufferers (92 %) had trouble following lessons, doing afternoon sport, and completing their homework.

Table 1 Triggers or factors aggravating headache

Trigger or aggravating factor	No.	%
Tiredness	43	72
Stress	25	42
Too little sleep	25	42
Hours in front of PC, TV, or video games	24	12
Menstruation	24	12
Too much sleep	19	10
Changes in the weather	16	8
Problems with parents	14	7
Problems with friends	13	6.5
Commuting by bus or car	12	6
Hunger	10	5
Alcoholic beverages (beer, wine)	10	5
Emotions	9	4.5
Problems with teachers	8	4
Smoking	6	3
Fear	5	2.5
Sweets	2	1

To relieve their headaches, 56 % took over-the-counter analgesics. None of the students who complained of strong, seriously debilitating headache (9) had ever taken anything to prevent it.

In response to the question of what ideas they had about the headache, 92 % gave no reply; 90 % had never read anything about headache or watched or listened to a program on TV or radio.

Discussion

To date, there are only few studies of headache at school, and our findings that 84 % of children suffer headaches at school are in line with other reports [8, 10–12]. We found more MH patients than in other studies but, although the percentage was lower, it was always higher than TTH [2, 10].

In the present study headache peaked during morning lessons or in the afternoon. This might be related to "school stressors", as mentioned in earlier studies of the impact of headache during schooltime, and the relationships between recurrent headaches and various psychological stressors [8, 11, 13, 14]. We too found that tiredness and stress were the most frequently reported triggers, followed by lack of sleep—probably all related; 92 % of headache sufferers said they had trouble following lessons

because of these problems. Among the MH sufferers, 20 % had medium–high MIDAS scores, similarly to previous case series [15].

Nearly 90 % had never tried to obtain information on their headaches, and more than half used OTC products for pain relief. None had ever consulted a specialist or a headache center to find about prevention or the most appropriate therapeutic strategies.

Educational program must be drawn to raise awareness on the suffering students about their condition and the possibility to face these diseases correctly. It is well demonstrated that such awareness can reduce the intake of drugs and can minimize the risk of developing a medication-overuse headache [16]. Moreover, taking the specific drugs can improve the course of migraine and can restore the normal functional condition [17].

Conclusions

This study highlights the need to promote headache education programs, starting at high school, to improve communication between teachers, family, physicians, and adolescent patients, with the goal of early, appropriate therapeutic intervention in order to avoid the need for self-medication, to improve the quality of life, and to prevent long-term or progressive headaches in adult life.

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

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ORAL COMMUNICATIONS

Headache in patients with idiopathic intracranial hypertension: a pilot study to assess applicability of ICHD-2 diagnostic criteria

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Abstract Headache is one of the most common symptoms of idiopathic intracranial hypertension (IIH). The aim of this study was to investigate the applicability of the diagnostic criteria for "Headache attributed to IIH" included in the current classification of headache disorders, particularly as far as the main headache features. A consecutive clinical series of IIH patients with demonstration of increased intracranial pressure by lumbar puncture in the recumbent position were enrolled. Among a total of 22 patients, headache was reported by 14. The proportion of patients reporting the main headache features required by diagnostic criteria were: 93 % for daily or nearly-daily occurrence; 71.5 % for diffuse/non-pulsating pain; 57 % for aggravation by coughing/straining. Thus, these three headache features, at least one of which is required for diagnosis of headache attributed to IIH, were present in the vast majority of our sample, suggesting that their inclusion should be regarded as appropriate. The analysis of our results may suggest possible changes in the current ICDH-2 criteria for headache attributed to IIH, based on the following considerations: the existence of remarkable differences as far as the relative frequency of each headache feature; the fact that diffuse and non-pulsating pain—included in the current classification as a single requirement—were not always found together; the high frequency of migrainous associated symptoms (nausea or photophobia–phonophobia were present in 71.5 % cases).

Keywords Idiopathic intracranial hypertension (IIH) · Headache · International Classification of Headache Disorders (ICHD-2)

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Introduction

Idiopathic intracranial hypertension (IIH) is the syndrome of elevated intracranial pressure in the absence of space occupying lesions or other brain disorders [1]. According to modified Dandy criteria for IIH [2], increased opening pressure on lumbar puncture and normal CSF composition together with absence of any known specific cause of increased intracranial pressure are the needed diagnostic requirements.

A diagnosis of IIH is a diagnosis of exclusion, after extensive diagnostic evaluations meant to rule out specific causes. Secondary intracranial hypertension occurs in a large variety of disorders, such as intracranial mass lesions (tumor, abscess), dural venous sinus thrombosis, traumatic brain injury, ischemic or hemorrhagic stroke, dural arteriovenous fistula, hydrocephalus [3]. An intracranial pressure at lumbar puncture in the recumbent position higher than 200 mmH_2O in adults is usually accepted as a marker of IIH diagnosis. Values higher than 100 mmH_2O and than 250 mmH_2O are required in young children and in obese patients, respectively.

Although IIH may be heterogeneous as far as clinical presentation, visual disturbances and headache are the most common symptoms [1–4]. For this reason operational

diagnostic criteria for "Headache attributed to IIH" have been included in the second edition of the international classification of headache disorders, the ICHD-2 [5] (Table 1).

The aim of this study was to investigate the applicability of the ICHD-2 criteria of headache attributed to IIH, particularly as far as the main clinical features of headache, in a sample of patients who were sent to our Neurology Department to verify a suspected diagnosis of IIH.

Patients and methods

We enrolled a consecutive series of patients attending our Neurology Department suspected to have IIH on the basis of their clinical history and/or previous ophthalmological examinations. The presence of headache, and its main characteristics, were systematically assessed and recorded. The presence of papilledema or other visual alterations was assessed by neuro-ophthalmologic examination. To rule out possible causative diseases, all patients underwent: lumbar puncture in the recumbent position, with measurement of intracranial pressure; CSF analysis; neurological and general examination; blood tests; MRI and MRI venography.

Results

Twenty-two consecutive patients (18 women, 4 men; mean age 38.5 years) were enrolled. Among them, 14 (63 %) reported headache. Papilledema was evident in all patients. Increased CSF pressure (<200 mmH_2O in normal weight patients, <250 in obese patients) was found in all the enrolled patients. A normal CSF chemistry was present in all cases. Intracranial mass lesions, dural venous sinus thrombosis, dural arteriovenous fistula, stroke, traumatic brain injury, hydrocephalus were absent in all the enrolled patients.

The progressive character of headache (i.e. a tendency to higher headache frequency during the course of illness) was present in all. As far as the main headache features, we found the following percentages: daily or nearly daily occurrence in 93 % cases (13 patients out of 14); diffuse/non-pulsating pain in 71.5 % (10 patients); aggravation by coughing/straining in 57 % (8 patients). Overall, at least one of these three features was present in all the studied patients: all the three features in 28.5 % (4 patients); two of them in 57.1 % of the sample (7 patients), and only one in 7.1 % (2 patients).

As far as the diffuse and non-pulsating quality of pain, these two characteristics were both present in eight patients, both absent in two, and only one feature was present in four patients.

Associated symptoms were present in many patients: nausea in 71.5 % (10 patients 14); photo-phonofobia in 71.5 % (in 10 patients); both nausea and photo-phonofobia in 21.4 % (in 3 patients).

Discussion

The main headache features required for diagnosis of headache attributed to IIH, were present in the vast

Table 1 International Headache Society diagnostic criteria for "Headache attributed to idiopathic Intracranial hypertension (IIH)" (code 7.1.1 of ICHD-2) [5]

A. Progressive headache with at least one of the following characteristics and fulfilling criteria C and D:
  1. Daily occurrence
  2. Diffuse and/or constant (non-pulsating) pain
  3. Aggravated by coughing or straining

B. Intracranial hypertension fulfilling the following criteria:
  1. Alert patient with neurological examination that either is normal or demonstrates any of the following abnormalities:
    a. Papilloedema
    b. Enlarged blind spot
    c. Visual field defect (progressive if untreated)
    d. Sixth nerve palsy
  2. Increased CSF pressure (>200 mmH_2O in the non-obese, >250 mmH_2O in the obese) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring
  3. Normal CSF chemistry (low CSF protein is acceptable) and cellularity
  4. Intracranial diseases (including venous sinus thrombosis) ruled out by appropriate investigations
  5. No metabolic, toxic or hormonal cause of intracranial hypertension

C. Headache develops in close temporal relation to increased intracranial pressure

D. Headache improves after withdrawal of CSF to reduce pressure to 120–170 mmH_2O and resolves within 72 h of persistent normalization of intracranial pressure

majority of our sample, suggesting that their inclusion should be regarded as appropriate.

However, the analysis of the results of this preliminary survey may suggest possible changes in the current ICDH-2 diagnostic criteria for "Headache attributed to IIH", based on the following considerations.

Remarkable differences were found as far as the three headache features, at least one of which is required for diagnosis, as daily occurrence was reported by almost all patients, while aggravation of headache by coughing/straining and the diffuse/non-pulsating quality of pain were present in a lower proportion (<60 and around 70 %, respectively).

In the current diagnostic criteria, the presence of diffuse/non-pulsating quality of pain is included as a single requirement. We note that the term "diffuse" may be not appropriate, and could be changed in "bilateral". Furthermore, the two characteristics could be split in two different features, as in our sample they were not always found together (4/14 patients reported only one of them).

Moreover, as far as the "progressive" nature of headache, this feature should be better defined. It is not clear if an episodic presentation before the daily occurrence of headache must be reported in patient's history, or if a progressive increase in headache severity is needed to make a diagnosis.

It is also interesting to note that some associated symptoms—the presence of which is not included among the current criteria—were present in many patients: nausea and-or photo-phonofobia were reported by around 70 % patients, although both symptoms were reported in 21.4 %. The high frequency of these "migrainous" accompanying symptoms, together with the pulsating quality and unilateral distribution of pain in some patients (in 28.5 and 14 %, respectively), may suggest a migraine-like presentation of headache in (a relevant proportion of) IIH patient, as previously reported [2, 4]. This topic is very intriguing, also considering the possible correlations between IIH and migraine progression postulated in the literature. Both clinical and instrumental findings indicate IIH—particularly IIH without papilledema—as a risk factor for migraine progression to chronic, often refractory forms [6, 7]. In fact, considering all the above-reported symptoms together with the usual daily occurrence of pain in 50 % of our IHH patients with headache, we note that a misdiagnosis of "primary" chronic migraine might be possible in patients who may in fact suffer from a "secondary" headache form.

We think that our findings will be useful in promoting further studies meant to assess headache characteristics on larger samples of IIH patients, to reach a better understanding of IIH and to evaluate a possible revision of current ICDH-2 diagnostic criteria for "Headache attributed to IIH".

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

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ORAL COMMUNICATIONS

Triptans: over the migraine

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Abstract Migraine is a chronic, recurrent, disabling condition that affects millions of people worldwide. Proper acute care treatment for migraineurs is based on triptans, a class of specific medications approved over 20 years ago. Triptans are serotonin (5-HT1B/1D) receptor agonists that are generally effective, well tolerated and safe. Seven triptans are available worldwide, although not all are available in every country, with multiple routes of administration, giving to doctors and patients a wide choice. Despite the similarities of the available triptans, pharmacological heterogeneity offers slightly different efficacy profiles. Triptans are not pain medications, they are abortive migraine medications which cannot prevent migraines. In addition to migraine attacks, triptans are also helpful for cluster headaches. If they are useful in other primary headaches rather than migraine and cluster headache it is yet to be addressed. In the literature there are only limited controlled clinical data to support a migraine-selective activity for triptans. Reports are available about efficacy of triptans to stop attacks of other types of primary headache, such as tension type headache, hypnic headache and other rare forms of primary headaches. On the other hand, sumatriptan failed to treat the indomethacin-responsive primary headache disorders like chronic paroxysmal hemicrania and hemicrania continua, nor was it effective in the myofascial temporal muscle pain or in atypical facial pain. Why triptans are effective in so different types of primary headaches remain unclear. Up to date, it is not clear whether the antimigrainous activity of the triptans involves an action only in the periphery or in the CNS as well. Probably we should consider triptans as "pain killers" and not only as "migraine killers". We clearly need additional studies on triptans as putative analgesics in well-accepted animal and clinical models of acute and chronic somatic pain.

Keywords Triptans · Migraine · Primary headache · Pain

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Introduction

On 28 December 1992, the FDA approved the first of a class of medications that many migraineurs would come to call "miracle drugs". That drug was the injectable form of sumatriptan (Imitrex®, Imigran®). The more technical name for this class of medications is triptans, selective serotonin receptor agonists. Triptans are not pain medications as we traditionally think of them. Triptans are termed abortive migraine medications. They are used to abort a migraine attack, to stop the attack itself and the associated symptoms. They cannot prevent migraines. The triptan family has grown since then. In Table 1 a list of the triptans approved in the US by the FDA are reported. Some of them were available in European countries before they became available in the US. Although these drugs belong to the same class and have many of the same characteristics, it is worth noting that they also have

differences. Because they are selective serotonin receptor agonists, they work on different serotonin receptors, and thus may produce different results and effects. Among triptans, data from clinical trials suggest that almotriptan is effective and well tolerated in the treatment of acute migraine pain. Almotriptan also have the highest sustained pain-free rate and the lowest adverse-event rate [1]. Among migraines, menstrual migraine is often reported to be more severe and more resistant to treatment than other migraines. Evidence of efficacy with acceptable safety and tolerability exists between triptans for sumatriptan 50 and 100 mg, rizatriptan 10 mg, combination of sumatriptan/naproxen 85 mg/500 mg, and as short term prophylaxis for frovatriptan and naratriptan [2]. Almotriptan demonstrated to be significantly more effective than placebo in women with menstrual related migraine attacks, with consistent efficacy in long-term follow-up [3]. In addition to migraine attacks, triptans are also sometimes helpful for other primary headaches such as cluster headaches (CH) [4]. Triptans in an injectable or intranasal preparation are a mainstay of acute CH treatment. The drug of choice for acute CH attacks is sumatriptan injected subcutaneously and more recently, intranasal zolmitriptan. The basis for the "apparent" selectivity of triptans in the treatment of migraine pain but not in other kinds of somatic pain is still not understood. Determining that exact mechanism of triptan action will likely provide important new insights into the pathogenesis of migraine and probably of other forms of primary headaches. At the probably end of the triptan "era", when new therapeutic options for migraine are overlooking and when the origin of migraine has yet to be known, we could come back to refer to clinical practice at the aim to discover other more off-label opportunities of triptans use in headache management. Some reports and clinical evidences could help us.

Off-label triptan uses

On occasion, healthcare providers may recommend a triptan for treating something other than migraine and CH. This is called an "off-label" use. At this time, using the oral or nasal spray triptans, other than sumatriptan and zolmitriptan to treat cluster headaches, would be an off-label use.

Tension type headache

It is a common clinical practice that for patients who experience both migraines and episodic tension headaches, a triptan can effectively relieve the pain of both headaches. Studies now dated have shown that the injectable form of sumatriptan may also relieve symptoms of tension type headache, exactly in episodic forms with associated migraines [5] and in chronic types [6]. The same authors 4 years later observed definitively that sumatriptan had no clinically relevant effect in the treatment of episodic tension type headache [7].

Triptan overuse headache

It is interesting to note another condition (or complication) in the headache and migraine industry—'Triptan overuse headaches' that is classified in ICHD-II as 'Medication overuse headache'. For many patients, the triptans were initially their best friend, but over time they needed to take another one in decreasing intervals, i.e. their effectiveness is decreasing or their pain is changing becoming more resistant to the initial dose. This is occurring perhaps because the sensitisation process is worsening. In 2006, the triptans sumatriptan 50 mg and naratriptan 2.5 mg were approved as over-the-counter (OTC) drugs in pharmacies in the UK and Germany, respectively. The implication of OTC triptan availability is medication overuse; therefore,

Table 1 Triptans in the US

US approval date	Triptan	Brand	Formulation
28 December 1992	Sumatriptan	Imitrex®, Imigran®	Injections
1 June 1995	Sumatriptan	Imitrex®, Imigran®	Tablets
26 August 1997	Sumatriptan	Imitrex®, Imigran®	Nasal spray
25 November 1997	Zolmitriptan	Zomig®	Tablets
10 February 1998	Naratriptan	Amerge®, Naramig®	Tablets
29 June 1998	Rizatriptan	Maxalt®, Maxalt-MLT®	Tablets and rizatriptan orally dissolvable tablets
13 February 2001	Zolmitriptan	Zomig-ZMT®	Zolmitriptan orally dissolvable tablets
7 May 2001	Almotriptan	Axert®	Tablets
8 November 2001	Frovatriptan	Frova®	Tablets
27 December 2002	Eletriptan	Relpax®	Tablets
30 September 2003	Zolmitriptan	Zomig®	Nasal spray
Not available in USA, only in Europe	Sumatriptan	Imitrex-USA, Imigran-Europe	Suppositories

patients should be warned of this and advised to use a triptan on fewer than 10 days per month. Pharmacists should be educated regarding migraine types and symptoms and on contraindications to triptans, so they are then able to discern the patients who should receive triptans and, as importantly, those who should not. Many reports about headache after frequent triptan use have been reported until the 1990s Limmroth et al. [8] ask whether drug-induced headache with triptans is a class effect. About a third of the patients described have reported daily tension type headache that was treated with non-steroidals and ergot derivatives, as well as triptans. They just report that of 11 patients who had increased frequency of headaches after the use of zolmitriptan or naratriptan, 9 benefited from withdrawal of treatment. Rebound headache has previously been described for sumatriptan [9, 10]. Mathew [11] reported the clinical experience at the Houston Headache Clinic (Houston, Texas, USA) suggesting that the frequency of triptan-induced rebound headache is actually very low. Of more than 1,000 patients given triptans in the past 5 years, about 2 % reported headaches that were related to or worsened with triptan use. These symptoms usually occurred in patients who had habitually long-lasting migraine or frequent interictal tension type headache. Psychological comorbidity such as depression, anxiety, and neuroticism were also associated with the tendency to use more triptans. He also noted that patients who have a tendency for multiple recurrences after triptans should be treated with adequate prophylactic medications rather than repeating the triptans. A recent Dutch population-based observational study [12] was used to assess the prevalence, demographics, risk factors, and costs of triptan overuse, defined as more than 30 (International Headache Society criteria) or 54 (stringent criteria) defined daily doses per 3 months. Triptans were used by 85,172 (1.3 %) people, of these, 8,844 (10.4 %; 95 % CI 10.2–10.6) were overusers by International Headache Society and 2,787 (3.3 %; 95 % CI 3.2–3.4) were overusers by stringent criteria. The triptan-specific odds ratios for the rate of International Headache Society overuse compared with sumatriptan were: 0.26 (95 % CI 0.19–0.36) for frovatriptan; 0.34 (95 % CI 0.32–0.37) for rizatriptan; 0.76 (95 % CI 0.68–0.85) for naratriptan; 0.86 (95 % CI 0.72–1.02) for eletriptan; 0.97 (95 % CI 0.88–1.06) for zolmitriptan; and 1.49 (95 % CI 1.31–1.72) for almotriptan. In the Dutch general population, 1.3 % used a triptan in 2005, of which 10.3 % were overusers. Frovatriptan, rizatriptan and naratriptan users had a lower level of overuse.

Post-traumatic headache

Post-traumatic headaches usually resemble migraines, psychiatric disorders such as depression are common comorbidities. Treatment of these headaches is based upon the treatment setting, whether the headaches are acute or chronic, the headache phenotype, and associated comorbidities. Management of post-traumatic headaches should be multidisciplinary whenever possible. No randomized, controlled clinical trials evaluating the efficacy of therapies for post-traumatic headaches have been completed. A recent study [13] shows that, among symptomatic therapies, triptans may be particularly effective in posttraumatic headaches in US service members who are deployed to or have returned from theaters of combat operations in Iraq and Afghanistan.

Other rare primary headaches

Hypnic headache

So far, no data from randomized placebo-controlled clinical trials are available for hypnic headache, so current treatment recommendations are based on single case reports and smaller open-case series. Patients affected are mostly elderly, an age where the drug tolerability is at least as important as their efficacy. For acute treatment, analgesics containing caffeine are also effective, but they may carry the risk of medication-overuse headache [14]. Triptans in majority of patients are off-label for age. They may be effective in single cases as reported by Schürks et al. [15].

Airplane headache

In recent years, there has been an increase in the reports indicating a form of headache that occurs during commercial aircraft travel. This headache, called "airplane headache" by some authors, is believed to be a new type of headache. The headache has very specific characteristics and all of the cases exhibited very stereotypical symptoms. It starts suddenly during the ascent and/or descent of the commercial aircraft, has a mean duration of 20 min, is usually unilateral and commonly localized to periorbital region. The headache is described to be severe, and has a stabbing or jabbing nature, and generally subsides in a short time. The main reports are by Turkish, Greek and Italian authors. The first case study included 5 patients with "airplane headache" [16]. Patients were recommended to use single dose of their drugs half an hour prior to flights. All of the patients had a good response to single dose triptan treatment and became headache-free during flights. This is the first study which puts forward the usefulness of the triptans as a safe treatment choice for airplane headache. Recently, other 22 cases who suffered from a headache that occurred during airplane travel have been

described [17]. Treatment strategies of airplane headaches are to date also controversial.

Post-dural puncture headache (PDPH)

PDPH is the most common complication of lumbar puncture, an invasive procedure frequently performed in the emergency room. Numerous pharmaceutical drugs have been proposed to treat PDPH but there are still some uncertainties about their clinical effectiveness [18]. Among these, sumatriptan use has been suggested but there is a lack of conclusive evidence for it. Among triptans, it is noteworthy that a non-randomized open-label study [19] suggested the efficacy of a 5-day treatment with oral frovatriptan 2.5 mg/die for the prophylaxis of PDPH in 50 hospitalized patients. Although innovative, these results need to be confirmed in a randomized, controlled, double-blind study.

Childhood headaches

Triptans' specifications show that use of these drugs is allowed only in patients aged over 18 years because available evidences are not sufficiently safe and reliable in pediatric ages. However, off-label use of triptans in childhood headaches are reported, exactly in the more common periodic syndrome of childhood as defined by ICHD-II classification, such as cyclic vomiting and abdominal migraine. The wide pediatric population affected by cyclic vomiting tested with sumatriptan has been recently reported by Japanese authors [20]. Sumatriptan was administered subcutaneously [(age $\times$ 4 + 20)/100 $\times$ 3 mg] in 11 patients and as a nasal spray (NS; 20 mg) in 5 patients. They concluded that sumatriptan has potential efficacy in treating patients with cyclic vomiting with an higher efficacy of the drug in attacks that occurred in cases with a family history of migraine compared to those without ($p = 0.0482$). Nasal sumatriptan (although not licensed for pediatric use) may be effective in relieving abdominal migraine attacks, as reviewed by Russel et al. [21] and more recently shown in other two pediatric case reports [22] suggesting that the mechanism of pain in abdominal pain-related functional gastrointestinal disorders could be similar to that of migraine, with probable central hypersensitivity, at least in a subset of cases.

Trigeminal neuralgia (TN)

Japanese authors reported that subcutaneous and nasal sumatriptan produced prompt and continuous analgesia without serious adverse reactions in patients with TN refractory to previous treatment. Kanai et al. [23] analyzed 24 patients with TN refractory to previous treatment randomized to receive subcutaneously either 3 mg (1 mL) of sumatriptan or 1 mL of saline placebo. Following a 7-day period, patients crossed over to receive the alternative treatment. Paroxysmal pain triggered by touching or moving the face was assessed with VAS before and 15 min after the treatment. The number of patients who described their pain as moderately or slightly better with VAS was 20 in the sumatriptan group and 1 in the placebo group. The effect of subcutaneous sumatriptan persisted for a median period of 7.9 h (range: 1–20 h). Same authors [24] tested other 15 patients with idiopathic TN suffering from painful paroxysms for at least 1 month. Each patient was injected with 1 mL of saline subcutaneously (placebo), followed 15 min later with subcutaneous sumatriptan (3 mg in 1 mL saline). This was followed the next day by oral sumatriptan (50 mg twice daily) for 1 week. With the same methods of the previous study, they observed that VAS did not change after saline, but significantly decreased after subcutaneous sumatriptan. Both 1 week after oral sumatriptan and 1 week after discontinuation of the drug, VAS scores resulted in a significant decrease from the baseline. The results indicate that subcutaneous injection followed by oral administration of sumatriptan produces other than a prompt response also a continuous analgesia in patients with TN. More recently [25] nasal sumatriptan has been demonstrated useful as an adjunctive therapy in 3 patients with idiopathic TN refractory to carbamazepine (CBZ), suggesting that this therapy might be suitable for patients for whom the CBZ dose cannot be increased, who are under poor pain control, and who are not candidates for nerve blocks or surgery.

Discussion and conclusion

Are therefore triptans migraine-selective?

Sumatriptan and the 'triptan' class of serotonin receptor subtype-selective drugs have a well-established efficacy in treating the pain of migraine [26]. Although sumatriptan was originally selected to target vasoactive properties thought to be fundamental to the etiology of migraine, other studies point to an action of triptans at several levels of the nervous system. Up to date however, it is not clear whether the antimigraine activity of the triptans involves an action only in the periphery or in the CNS as well. Because sumatriptan is hydrophilic, it penetrates the blood-brain barrier poorly, suggesting a peripheral site of action. On the other hand, it has been proposed that the barrier is compromised in migraineurs, so a CNS site of action has not been ruled out. However, 5-HT1B and 5-HT1D receptors are not only localized to the trigeminal afferents of the head but are found throughout the body [27, 28]. Evidences

of triptans' specificity remains controversial. On the one hand, sumatriptan failed to treat, in primis, episodic tension type headache, in secundis, all the indomethacin-responsive primary headache disorders, such as chronic paroxysmal hemicrania and hemicrania continua [29], nor was it effective in a study of myofascial temporal muscle pain [30], or in a small series with atypical facial pain [31]. On the other hand, cluster headache is a distinct primary headache disorder that clearly responds to triptans [4]. Other types of primary and secondary headaches, with likely different pathogenetic basis, although rare in their prevalence, and supported by little evidences, as we reviewed, may respond to triptans. Furthermore, nociceptive thresholds are modulated by sumatriptan in patients with extracranial allodynia during a migraine attack, but the mechanism of action for that change is presumed to be due to the alteration of the underlying central mechanism of migraine, rather than a direct action on nontrigeminal-nociresponsive systems [32]. In contrast, evidence for the nonselective activity of triptans was reported in an inflammatory model of pain, where sumatriptan dose-dependently reduced behavioral signs of hyperalgesia after carageenan injection of the mouse hindpaw [33]. One hypothesis for the selectivity of triptan action arose from studies of the distribution of 5-HT1D receptor in primary afferent terminals. Rather than being localized on the plasma membrane, the receptors are concentrated in the dense core vesicles that store peptide neurotransmitters [27]. This model of activation-dependent 5-HT1D receptor availability is consistent with the fact that triptans do not prevent the pain of migraine, and predicts that triptans would only be effective in experimental models of pain in which a prior stimulus has activated nociceptors and externalized the triptan receptor to the presynaptic membrane. Beside these controversial experimental evidences, the existence of a pure triptan medication overuse headache raises a relevant issue. We do not know whether drug-induced headache indicates a neuronal or vascular mechanism, a threshold or sensitivity effect, or even an allergic or immunological response. Recently, it has been shown that overuse of these medications could induce neural adaptations that result in a state of latent sensitization, which might increase sensitivity to migraine triggers [34]. The latent sensitization could provide a mechanistic basis for the transformation of migraine to medication overuse headache. The fact that a very small percentage of patients may show paradoxical response to triptans should not prevent patients and physicians from continuing to use triptans. Actually, triptans are still the best therapeutic option to treat migraine and cluster headache attacks and perhaps, waiting new pharmacological developments, we will tend to discover new use, also off-label uses of triptans in others primary headaches. What is clearly needed is a study of triptan treatment in patients with a well-defined non-cranial somatic pain disorder, in which nociceptive thresholds can be assessed in addition to self-reported pain relief scores.

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

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ORAL COMMUNICATIONS

Possible correlations between blood pressure, primary headaches and cutaneous allodynia

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Abstract Following an allostatic perspective, episodic migraine (M) may be considered as an adaptive behavioural response to endogenous or exogenous stressors, while its progression to a daily or nearly daily form (chronic migraine) may represent the failure of adaptive strategies. Multiple factors may enhance the progression/chronification of M, and among these the presence of cutaneous allodynia (CA) as well as alterations in blood pressure and in sleep. The working hypothesis of the study was that subjects with M, and particularly those with CA, could show a tendency towards high blood pressure levels and/or to alterations in the circadian rhythm of blood pressure. We studied 235 subjects consecutively attending a centre for blood pressure control for a blood pressure 24 h monitoring. Headache diagnosis was made according to the ICHD-II criteria. The presence of CA was evaluated through a semi-structured ad hoc questionnaire. Blood pressure 24 h monitoring was performed by an ambulatory blood pressure monitor (Space Labs) with its ad hoc software. Seventy-eight subjects had a history of headache (mean age 54.0 ± 12.4 years, 18 men and 60 women); 56 of them had M, 22 had tension-type headache; among them, CA was found in 24/56 subjects with M, and in 6/22 with tension-type headache; 157 subjects did not suffer from headache (mean age 60.5 ± 11.5 years, 99 men and 58 women). No significant difference was observed between headache subjects and subjects without headache in terms of mean systolic and diastolic pressure, neither in the M nor in tension-type subgroups. With regard to the circadian rhythm of blood pressure, the physiological reduction during night (dipping) was more evident among headache subjects than in subjects without headache; this border-line difference was more strongly significant in subjects with CA than both non-headache ($p = 0.003$) and non-CA ($p = 0.05$) ones. The difference between allodynic and non-allodynic subjects was present also in the M sub-group (7 dippers out of 32 non-allodynic migraineurs vs. 12 dippers out of 24 allodynic migraineurs, $p = 0.03$) notwithstanding the reduction of the sample size. Despite the initial hypothesis, subjects with primary headaches did not show differences in terms of mean blood pressure values and they showed a more physiologic blood pressure daily rhythm than those without headaches. Also the presence of CA, a marker of progression to chronic headache forms, was associated neither with hypertension nor with increased frequency of loss of dipping. M, particularly when associated with allodynia, may improve breathing during nocturnal sleep and consequently counteract possible blood pressure alterations, suggesting an allostatic function of allodynic headache.

Keywords Headache · Migraine (M) · Blood pressure · Cutaneous allodynia (CA) · Dippers

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Introduction

Following an allostatic perspective, episodic migraine (M) may be considered as adaptive behavioural response to endogenous or exogenous stressors, while its progression to

a daily or nearly daily form (chronic migraine) may represent the failure of adaptive strategies and its transformation in a more disabling and difficult to treat condition. This transformation includes a change of head pain pattern and characteristics of associated symptoms that may reflect functional and possibly structural modifications of the neuronal circuitry involved in M patho-physiology.

Multiple factors which could enhance the progression/chronification of M are under investigation, and among these the presence of cutaneous allodynia (CA) as well as alterations in blood pressure and in sleep pattern may have a role. In parallel, a number of physiological aspects seem to be influenced by M and its course, including sleep and blood pressure.

A number of studies found an association between hypertension and M chronification and this observation induced the hypothesis that hypertension may probably modify the vascular wall and the endothelial function in the cerebral vasculature.

The working hypothesis of the study was that subjects with M, and particularly those with CA, could show a tendency towards high blood pressure levels and/or to alterations in the circadian rhythm of blood pressure.

The main aim of this study is to assess the relationships between the presence of primary headaches (and particularly M) and of headache-related CA with blood pressure pattern.

We planned to evaluate: (a) the presence of headache in subjects who underwent a 24 h monitoring of the blood pressure; (b) the distribution of different kinds of headache and CA in this population; (c) the blood pressure pattern in different kinds of headache.

Materials and methods

The study included 235 subjects consecutively attending the Centre for blood pressure control of the Luigi Sacco Hospital in Milan for a blood pressure 24 h monitoring.

History of headache was evaluated in each subject and headache diagnosis was made according to the ICHD-II criteria [1].

The presence of CA was evaluated through a semi-structured ad hoc questionnaire previously used by our group in other studies [2, 3]. The questionnaire investigates if the subject experiences abnormal scalp sensitiveness and/or discomfort during headache episodes and which daily activities enhance/induce this symptom. All the enrolled subjects were asked to give written yes/no responses to written questions as follows: (1) Has the subject experienced abnormal scalp sensitivity or discomfort during headache attacks? If yes, does this abnormal sensitivity or discomfort arise from (a) touching head skin; (b) touching hair; (c) combing hair; (d) brushing hair; (e) wearing glasses; (f) using a hair-band, curlers or elastic for forming a ponytail; (g) lying with head resting on the pain side? Subjects replying yes to the first question and at least to one of these questions (a–f) were considered to have headache-associated CA.

Blood pressure 24 h monitoring was performed by an ambulatory blood pressure monitor (Space Labs) with its ad hoc software.

Results

Headache and CA distribution

Among the 235 enrolled subjects, 157 did not suffer from headache (mean age 60.5 ± 11.5 years, 99 men and 58 women); 78 had a history of headache (mean age 54.0 ± 12.4 years, 18 men and 60 women). Among them, 56 had M (mean age 52.3 ± 11.6 years, 11 men and 45 women) and 22 had tension-type headache (mean age 58.4 ± 13.5 years, 7 men and 15 women). Among headache subjects, CA was found in 24 out of 56 subjects with M, and in 6 out of 22 with tension-type headache (Table 1).

Mean systolic and diastolic pressure in the cohort

No significant difference was observed between headache subjects and subjects without headache in terms of mean systolic and diastolic pressure, neither in the M nor in the tension-type subgroups. Also after grouping by presence of CA, no difference was found (Table 2).

Circadian rhythm of the blood pressure

The physiological reduction of blood pressure during night (dipping) was more evident among headache subjects

Table 1 Distribution of headache and cutaneous allodynia (CA)

Subjects studied by blood pressure 24 h monitoring	No.	M/F	M (%)	F (%)	Mean age (years)
Total	235	117/118	49.8	50.2	58.3
Without headache	157	99/58	63.0	37.0	60.5
Headache subjects					
Total	78	18/60	23.0	77.0	54.0
Migraine	56	11/45	19.6	80.4	52.3
With CA	24	3/21	12.5	87.5	50.1
Without CA	32	8/24	25.0	75.0	53.9
Tension-type headache	22	7/15	31.8	68.2	58.4
With CA	6	1/5	16.6	83.4	63.8
Without CA	16	6/10	37.5	62.5	56.5

Table 2 Distribution of mean blood pressure values in different diagnostic groups

	Nocturnal systolic arterial pressure	Nocturnal diastolic arterial pressure	Diurnal systolic arterial pressure	Diurnal diastolic arterial pressure
Non-allodynic TTH	114.1	65.3	128.5	78.5
Allodynic TTH	115.0	66.0	137.3	83.5
Non-allodynic M	118.5	70.3	130.6	81.9
Allodynic M	120.0	71.4	133.4	85.0
Non-headache subjects	118.8	69.4	135.9	81.1

Table 3 Prevalence of physiologic dipping among different diagnostic groups

Allodynic headaches show the largest prevalence of correct circadian rhythm of blood pressure

	Dippers (*N*)	Non-dippers (*N*)	Total (*N*)	Dippers (%)	Non-dippers (%)
Allodynic headache	18	12	30	60	40
Non-allodynic headache	16	32	48	33	67
Non-headache	50	107	157	32	68
Allodynic M	12	12	24	50	50
Non-allodynic M	7	25	32	22	78
Allodynic TTH	6	0	6	100	0
Non-allodynic TTH	9	7	16	56	44
Non-headache	50	157	157	32	68

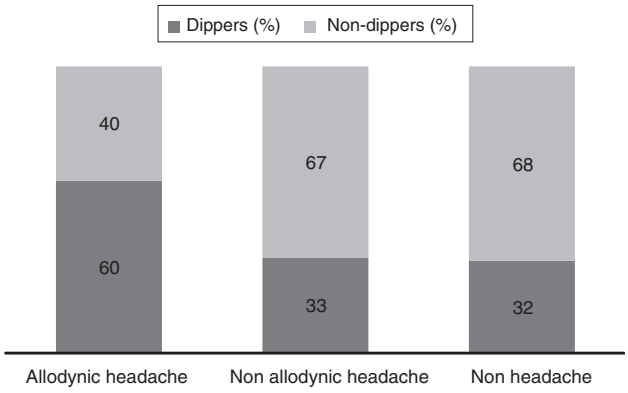

Fig. 1 Distribution of dipping among different diagnostic groups

(34 dippers out of 78 subjects) than in subjects without headache (50 dippers out of 157). The difference was highly significant in subjects with CA (18 dippers out of 30) than both non-headache (50 dippers out of 157, $p = 0.003$) and non-CA (16 out of 48, $p = 0.05$) ones (Table 3; Fig. 1).

The difference between allodynic and non-allodynic subjects was present also in the M sub-group (7 dippers out of 32 non-allodynic migraineurs vs. 12 dippers out of 24 allodynic migraineurs, $p = 0.03$) notwithstanding the reduction of the sample size.

Discussion

The initial hypothesis was that arterial hypertension or the loss of physiological dipping might be one of the causes of migraine transformation. Despite this initial hypothesis, subjects with primary headaches did not show differences in terms of mean blood pressure values and they showed a more physiologic blood pressure daily rhythm than those without headaches. Also the presence of CA, a marker of progression to chronic headache forms, was neither associated with hypertension nor with an increased frequency of loss of dipping. On the contrary, subjects primary headaches, and particularly allodynic ones, seem to maintain a more physiologic blood pressure daily rhythm than those without allodynic headaches.

Our group recently demonstrated [4] that episodic migraine, even when allodynia is present, is associated with better respiratory parameters during night, probably preventing apnoeas by reducing deep sleep. Obstructive apnoeas during sleep are associated with systemic hypertension and alterations of the dipping. [5]. On the basis of these evidences we may suggest that migraine, particularly when associated with allodynia, may improve breathing during nocturnal sleep and consequently counteract possible blood pressure alterations.

Even considering the possibility of a selection bias (we studied subjects attending a blood pressure control centre for a blood pressure 24 h monitoring), our results suggest a possible allostatic function of allodynic headache.

Conflict of interest There is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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ORAL COMMUNICATIONS

Alcohol as a dietary trigger of primary headaches: what triggering site could be compatible?

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

Abstract Alcoholic drinks (AD) have been known as migraine triggers in about one-third of migraine patients in retrospective studies. We have reviewed the studies concerning the role of AD in triggering the various types of primary headaches published after the International Headache Society classification of 1988. There are many studies showing that AD are triggers of migraine without aura (MO), migraine with aura (MA), cluster headache (CH) and tension-type headache (TH). About one-third of MO and half of CH patients reported AD as trigger factors. Some studies show that AD are triggers in MA and TH in a similar percentage to that found in MO, but there are also discordant findings. There are sparse reports that AD are also triggers of less frequent types of primary headache such as familial hemiplegic migraine, hemicrania continua and paroxysmal hemicrania. The mechanism of alcohol-provoking headache is debated and should be compatible with the principal pathogenetic theories of primary headaches. If AD are capable of triggering practically all primary headaches, they should act at a common pathogenetic level. Vasodilatation is unlikely to be compatible as common mechanism. An action at cortical or more likely at subcortical level is plausible.

Keywords Alcohol · Trigger factors · Migraine · Headache · Pathogenesis

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Introduction

Many retrospective studies show that alcoholic drinks (AD) act as migraine triggers at least occasionally in about one-third of migraine patients [1]. In the International Headache Society (IHS) classification, alcohol was considered a possible migraine and cluster headache (CH) trigger but no mention of an alcohol interference with tension-type headache (TH) was reported [2]. However, some studies report that AD are triggers of TH also [3]. We have reviewed the studies concerning the role of AD in triggering the various types of primary headaches published after 1988 first edition of IHS classification. The possible correlation of the results with the pathogenesis of the primary headaches was discussed.

Clinical evidences

A large number of retrospective studies performed in Europe and America reported AD as trigger factors in more than 20 % of migraine without aura (MO) patients (the average percentage of 14 studies was 31.9 %). However, there are studies reporting lower percentages. In fact, in India, Japan and Turkey, the percentages of alcohol or wine as MO trigger were very low (0, 1 and 6 % respectively), perhaps depending of the degree of alcohol habits, that is to a lower rate of alcohol consumption or a different beverage strength. Prospective studies provide evidence for the limited importance of alcohol in the precipitation of migraine [4, 5].

Seven studies report AD as triggers of migraine with aura (MA), four of them in a percentage similar to that found in MO patients (about 30 %), while in two studies in a much lesser percentage. In the more recent detailed study

in patients having both current MA and MO attacks (one or more attacks within the last year), AD are reported as trigger factors more frequently in MO (51 %) than MA (40 %) attacks [6].

Five studies report AD as TH triggers in about the same percentage (30 %) of MO patients. However, other studies show sensitivity to AD in only 0–2 % of patients with pure TH.

AD are triggers of attack in chronic CH and in episodic CH only during bouts, in more than 50 % of patients (the average percentage of six studies was 53.8 %).

There are sparse reports that AD are also triggers of less frequent types of primary headache such as familial hemiplegic migraine (FHM), hemicrania continua and paroxysmal hemicrania. A recent Danish study reports that FHM share environmental migraine triggers with MA and MO, enclosed AD [7].

Discussion

That alcohol is a common trigger of headache in the principal types of primary headaches may suggest that these headaches can share a pathogenetic mechanism and that this trigger acts at the start of the pathway involved in headache provocation. In fact, it seems unlikely that AD may act with different mechanisms in different forms of headache but with similar phenotypic features.

Current understanding of pain neurobiology points to a role for meningeal nociceptors activation in migraine pain through inflammatory/vasodilatory mechanism. Cortical spreading depression (CSD) is the putative electrophysiological event underlying migraine aura and has been proposed as the mechanism responsible for the activation of the migraine pain pathway. Migraine triggers, enclosed AD, can theoretically provoke CSD, which can theoretically be responsible for MA, but also for FHM and MO. But at what level AD trigger TH, CH and other trigeminal autonomic cephalalgias? A unitary hypothesis suggests that migraine triggers promote the headache by the activation of subcortical distinct neuronal pathways originating in several brain nuclei, but convergent into parasympathetic trigeminal innervation, which if activated results in meningeal release of vasoactive and algesic mediators capable of activating meningeal nociceptors [8].

In theory, an alternative peripheral trigger mechanism, that is a direct meningeal nociceptor stimulation through vasodilatation and/or inflammatory mediators could also provoke migraine pain. Animal studies report that alcohol, mimicking capsaicin, provokes neurogenic inflammation in the trigeminovascular system and vasodilatation of meningeal vessels through transient receptor potential vanilloid 1 (TRPV1) activation and CGRP release [9]. While high alcohol blood concentrations lead to vasoconstriction, lower doses have been found to have both vasodilative and vasoconstrictive activities on the cerebral vessels. If the vasodilatation at the trigeminovascular level can theoretically be compatible with MO and CH provocation, how can it be the trigger of aura and subsequent migraine pain or TH pain? Unless migraine aura is provoked by vasoconstriction and TH is due to vasodilatation a direct mechanism at vascular level is difficult to sustain.

It was also proposed that migraine triggers cause cortical activation, which, similar to CSD, disinhibit trigeminovascular sensation through brainstem nuclei, involving a serotonergic mechanism. The pain signal was suggested as a "false alarm" occasioned by some defect in pain perception or modulation [10], a mechanism previously theorized and called "functional deafferentation" [11]. Another question, previously discussed, is if alcohol per se or some components of AD are responsible for headache provocation. In fact, alcohol has been reported to have analgesic effect in animal and human studies. Experiments with "alcohol clamp", a method of infusing alcohol to achieve and maintain a target breath/blood alcohol level for a prolonged time (3 h), do not report migraine within the 8 h of the typical session study [see 12]. Acute intake of ethanol acts as a central nervous system depressant. In fact, ethanol infusion decreased the propagation rate of CSD, indicating a decline of tissue excitability and in the initiation mechanisms of CSD [13]. The cited alcohol activities are not easily compatible with headache triggered by AD, and a different activity of alcohol itself or of the other components of AD has been debated to be involved in headache provocation [1, 12]. The action of alcohol on central pain circuits, in particular through serotonin (5-HT) release, has been suggested, in agreement with the migraine-provoking effect of 5-HT releasing drugs [12, 14].

In conclusion, AD have been reported to trigger the principal types of primary headaches. While the results in MO and CH are in relative agreement, those in MA and TH are sometimes discordant. However, if the results in MA and TH are confirmed in a large study, without the concomitant presence of MO in these patients, a unitary hypothesis of AD trigger activity should be the consequence. In this case, a direct action at the vascular system is hardly compatible with TH but also with MA, and an action at subcortical level is more plausible.

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

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ORAL COMMUNICATIONS

Acupressure in the control of migraine-associated nausea

Gianni Allais · Sara Rolando · Ilaria Castagnoli Gabellari · Chiara Burzio · Gisella Airola · Paola Borgogno · Paola Schiapparelli · Rita Allais · Chiara Benedetto

Abstract Migraine is a disabling neurological disorder, aggravated by accompanying symptomatology, such as nausea. One of the most interesting approaches to nausea adopted by traditional Chinese medicine is the stimulation of the acupoint PC6 *Neiguan.* Actually there are no studies in medical literature as to the efficacy of treating PC6 acupoint for gastrointestinal symptoms in migraine attacks. Our study aimed at verifying if pressure applied to the acupoint PC6 was effective on nausea during migraine. Forty female patients suffering from migraine without aura were enrolled, if nausea was always present as accompanying symptomatology of their migraine. The patients were treated randomly for a total of six migraine attacks: three with the application of a device, the Sea-Band® wristband, which applies continual pressure to the PC6 acupoint (phase SB), and three without it (phase C). The intensities of nausea at the onset, at 30, 60, 120 and 240 min were evaluated on a scale from 0 to 10. The values were always significantly lower in phase SB than in phase C. Also the number of patients who reported at least a 50 % reduction in the nausea score was significantly higher in phase SB than in phase C at 30, 60 and 120 min. Moreover, the consistency of the treatment (response in at least two out of three treated attacks) was reached in 28 % patients at 60 min; in 40 % at 120 min and 59 % at 240 min. Our results encourage the application of PC6 acupressure for the treatment of migraine-associated nausea.

Keywords Migraine · Nausea · PC6 acupressure

Abbreviations

CINV Chemotherapy-induced nausea and vomiting
PONV Postoperative nausea and vomiting

Introduction

Migraine is a disabling neurological disorder considered by the World Health Organization as the 19th leading cause of all years lived with disability among both males and females of all ages, and as the 12th leading cause of years lived with disability among females of all ages [1]. Apart from pain, the disability caused by migraine is aggravated by accompanying symptomatology, such as gastro-intestinal symptoms, the most common being nausea and vomiting, to such an extent that their presence is one of the diagnostic criteria for migraine [2]. A telephone interview survey of 500 self-reported migraine sufferers found that nausea occurred in more than 90 % of all migraineurs; nearly one-third of these had nausea during every attack. Vomiting occurred in almost 70 % of all migraineurs; nearly one-third of these vomited in the majority of attacks. Indeed, 30.5 % of those who had nausea, reported that it interfered with their ability to take their oral migraine medication [3]. The American Study II stated that 73 % of the migraineurs studied reported to have suffered from nausea during attacks and that 29 % had vomited [4].

One of the most interesting approaches to nausea adopted by traditional Chinese medicine and, in particular,

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by acupuncture is the stimulation of the acupoint PC6 *Neiguan.* Indeed, there is documented evidence as to the efficacy of stimulating this point to alleviate chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV) and motion sickness, both with acupuncture and acupressure. However, to the best of our knowledge, there are no studies in indexed medical literature as to the efficacy of treating PC6 acupoint for gastrointestinal symptoms in migraine attacks and particularly for nausea. Therefore, our preliminary study aimed at verifying if pressure applied to the point PC6 was effective on the presence of nausea during migraine attacks.

Patients and methods

A total of 40 female patients were enrolled into this study, after having given their informed consent, and all were suffering from migraine without aura, diagnosed according to the criteria established by the International Classification of Headache Disorders (ICHD-II) [2]. The patients were examined at the Women's Headache Center, Department of Gynaecology and Obstetrics of Turin University. Inclusion criteria were: at least two migraine attacks per month for a 1-year period before enrollment; no more than 15 days of pain per month. The study had the maximum duration of 3 months. None of the patients were on prophylactic therapy, but were allowed to continue taking their usual symptomatic treatment. The patients' medical history had to include the presence of nausea as accompanying symptomatology of their migraine, documented by a diary noting at least 1 month of attacks with nausea, prior to the inclusion in the study. Subjects taking antiemetics to control their nausea, whether as a single product or present as a compound in a combination product for the control of migraine, were excluded from the study. The patients enrolled were asked to fill in a dedicated diary recording the details of the length and intensity of the migraine attacks along with the accompanying symptomatology, paying particular attention to the presence of nausea. A device known as the Sea-Band® was given to the patients to control their nausea. The Sea-Bands® are elastic wristbands with a 1 cm protruding round plastic button; these devices apply continual pressure to the PC6 acupuncture point with the aim of decreasing, or completely eliminating nausea (Fig. 1). The PC6 point, also called *Neiguan*, is located on the anterior surface of the forearm, 3 fingers widths up from the first wrist crease and between the tendons of the flexor carpi radialis and palmaris longus. The Sea-Bands® were applied bilaterally on both wrists on the *Neiguan* point, starting from the onset of the migraine attack and left in place for no less than 4 h, or for the whole attack period.

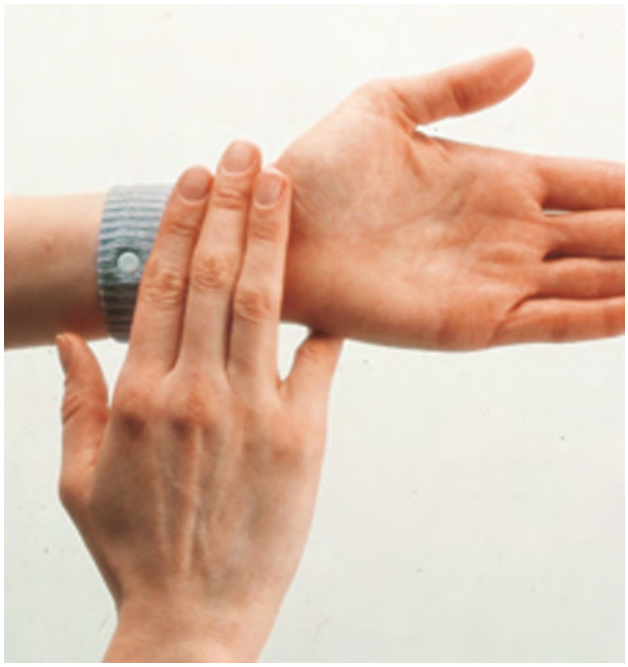

Fig. 1 The localization of the point PC6 *Neiguan* and the correct positioning of the Sea-Bands®

The patients were asked to document a total of six migraine attacks: three without the use of the Sea-Band® wristbands (phase C, control) and three with the application of the Sea-Bands® (phase SB). The sequence of the treatment given for the attacks (with, or without Sea-Bands®) was chosen at random according to a scheme provided by the computer and was applied to each single patient.

The section of the diary provided that covered the symptom of nausea was detailed to include information as to the time of symptom onset and symptom resolution, the intensity of nausea at the onset (T0), at 30 (T1), 60 (T2), 120 (T3) and 240 (T4) minutes evaluated on a scale from 0 to 10, where 0 indicated no nausea and 10 the maximum sensation of nausea.

Diary analysis was carried out by an impartial operator who did not know in which attacks the Sea-Bands® were used or not. In this preliminary study, the analysis of diaries is focused only on nausea symptomatology.

The average values of nausea in phases C and SB were calculated at different times throughout the study and a statistical evaluation of the differences between the values obtained in T0, T1, T2, T3 and T4 in the two groups studied was performed using a non-parametric Friedman test for repeated measures.

Moreover, a non-parametric Wilcoxon test for paired data was always performed for each level of the variable ''time'' to evaluate the difference between phase C and phase SB. This test also took into consideration the average intensity of the three attacks in each of the two phases. All values given in the following text are reported as arithmetic

means (±SEM). A Chi square test was applied for proportions. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software program.

Results

Only 32 patients (mean age 39.65 years, range 19–61) completed the study. Four patients were lost to follow-up, three handed over a diary with incomplete, unreliable data and one patient did not suffer from any migraine attacks in the 3-month observation period. The Friedman test for repeated measures showed a highly statistically significant reduction in the intensity of nausea in the SB group ($p < 0.001$) during treatment (at T1, T2, T3 and T4).

The Wilcoxon test for paired data showed that the nausea intensities were significantly higher in phase C than in phase SB (Fig. 2): after 30 min (T1 C 5.55 ± 0.36 vs. T1 SB 4.6 ± 0.40, $p = 0.006$), 60 min (T2 C 4.93 ± 0.33 vs. T2 SB 3.11 ± 0.40 $p < 0.001$), 120 min (T3 C 3.48 ± 0.35 vs. T3 SB 1.89 ± 0.31 $p < 0.001$) and 240 min (T4 C 2.05 ± 0.28 vs. T4 SB 0.93 ± 0.23 $p < 0.001$). There was no difference between groups at T0 (T0 C 5.96 ± 0.38 vs. T0 SB 6.36 ± 0.35; $p = 0.276$).

The number of patients who reported having had at least a 50 % reduction in the nausea score was: 0/32 at 30 min in phase C and 7/32 in phase SB (Chi square test: $p = 0.16$ RR 0.43; CI 95 % 0.32–0.58); 1/32 at 60 min in phase C and 15/32 in phase SB (Chi square test: $p < 0.001$ RR 0.37, CI 95 % 0.25–0.56); 11/32 at 120 min in phase C and 23/32 in phase SB (Chi square test: $p = 0.003$ RR 0.44, CI 95 % 0.24–0.80); 21/32 at 240 min in phase C and 27/32 in phase SB (Chi square test: $p = 0.083$ RR 0.55, CI 95 % 0.25–1.1). Moreover, when the consistency of the treatment (response in at least two out of three treated attacks) is taken into consideration, it was reached: in 9 patients (28 %) at 60 min; in 13 (40 %) at 120 min and in 19 (59 %) at 240 min. Noteworthy, the nausea was significantly reduced by acupressure in 3/3 attacks: in 5/32 patients (15 %) at 60 min; in 10/32 (31 %) at 120 min and in 17/32 (53 %) at 240 min.

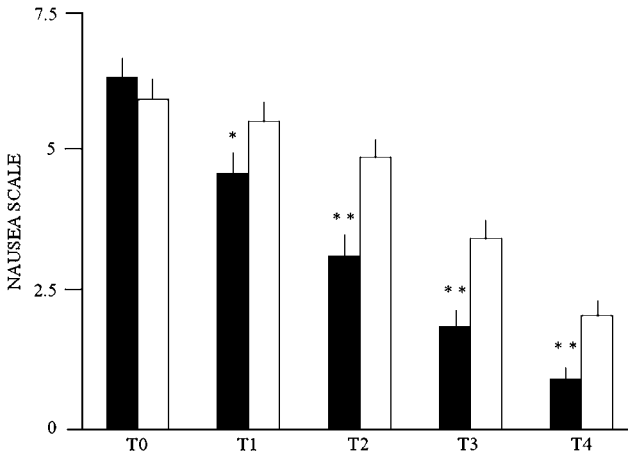

Fig. 2 Average values of nausea score before treatment (T0), after 30 min (T1), after 60 min (T2), after 120 min (T3), after 240 min (T4), in phase SB (*black columns*) and in phase C (*white columns*). Non-parametric Wilcoxon test for paired data at T0, T1, T2, T3 and T4: at T0 $p = 0.276$, n.s.; at T1 $*p = 0.006$; at T2, T3 and T4 $**p < 0.001$

Discussion

Nausea is one of the most invalidating symptoms associated with migraine attacks. Some studies have reported that nausea was present in 73 to more than 90 % of the subjects studied and that almost one-third of these experienced nausea during every attack. Moreover, 30.5 % of the subjects who reported nausea indicated that its severity even interfered with their ability to take their oral migraine medication [3, 4].

Traditional Chinese medicine and especially acupuncture, stimulates some points that can be considered extremely valid from the point of view of nausea and/or vomiting control. In particular, the treatment of the acupoint PC6 *Neiguan* may be applied to this aim, even with the application of acupressure alone, as has been validated by various studies. International literature reports numerous studies on the efficacy of stimulating the acupuncture point PC6 and its capacity to reduce nausea under various clinical conditions. A Cochrane Review on PONV concluded by stating that, compared with sham treatment, acupoint stimulation significantly reduces nausea (RR 0.71, 95 % CI 0.61–0.83) and the need for rescue antiemetics (RR 0.69, 95 % CI 0.57–0.83) [5]. From a Cochrane Review on CINV, it emerged that acupressure is effective for both mean and worst acute nausea severity, and, therefore, acupressure is able to offer a no-cost, convenient, self-administered intervention for chemotherapy patients to reduce acute nausea [6].

On the basis of the data obtained in this study, the application of acupressure for the control of nausea during a migraine attack seems to be justified. Indeed, the application of the Sea-Bands® on the acupoint PC6 Neiguan was observed to be effective in the control of nausea. The average nausea scores drop in the SB phase from 6.36 ± 0.35 in T0, to 4.60 ± 0.39 in T1, to 3.11 ± 0.40 in T2, to 1.88 ± 0.31 in T3 and to 0.92 ± 0.22 in T4. At each time step taken into consideration after the application of the Sea-Bands®, there was a statistically significant improvement over the non-treated phases. Moreover, there was a high percentage of responders to the treatment: i.e. 46.8 % at 60 min; 71.8 % at 120 min; 84.3 % at 240 min

with a consistent response over time. Even when the fact that our study is both preliminary and open is taken into consideration, the results obtained seem to be encouraging and advocate the continuous application of PC6 acupressure in all migraine attacks with the accompanying symptom of nausea. Further controlled studies are, of course, required to validate the findings of this study.

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Conflict of interest None.

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ORAL COMMUNICATIONS

Obsessive–compulsive aspects as predictors of poor response to treatments in patients with chronic migraine and medication overuse

M. Curone · D. D'Amico · G. Bussone

Abstract Patients with chronic migraine (CM) and medication overuse (MO) have a high frequency of psychiatric comorbidity or psychopathological traits, the presence of which may have important implications for the course of the CM and the MO, both for response to treatment and possible relapses. Overuse of symptomatic drugs is regarded as one of the most important risk factor for the transformation of episodic migraine into CM and drug-seeking tendency due to fear of headache in chronic migraine patients shares with obsessive–compulsive disorder (OCD) the compulsive quality of the behavior. Aim of this study was to review the clinical history of a sample of CM patients with MO in which an obsessive–compulsive trait was identified, performing a comparison with a sample of patients without obsessive–compulsive trait. We selected 14 patients with positivity to Spectrum Project OBS (obsessive–compulsive disorder) questionnaire and other 14 patients with negativity to the same tool from among a sample of patients who were enrolled in a previous study on the psychopathological profile of patients suffering from CM with MO. According to data obtained from the clinical records referring to the previous 5 years, patients with OBS questionnaire positivity showed a worse clinical course and a tendency to early relapse in MO after symptomatic medication withdrawal. Our results show that the comorbidity of OCD should be always evaluated in patients with CM and MO as it may play a relevant role—particularly if not treated—among the risk factors favoring the progression of episodic migraine to the chronic form, and/or the tendency to a pathological behavior that prompts the overuse of symptomatic medications.

Keywords Obsessive–compulsive disorder (OCD) · Subclinical · Chronic migraine (CM) · Medication overuse (MO) · Treatment

Introduction

Patients with chronic migraine (CM) and medication overuse (MO) have a high frequency of psychiatric comorbidity or psychopathological traits [1–3]. The presence of psychiatric comorbidity, especially obsessive–compulsive symptomatology may have important implications for the course of the CM and the MO, both for response to treatment and possible relapses. Obsessive–compulsive disorder (OCD) as well as subclinical obsessive–compulsive disorder is mentioned in the spectrum of comorbid conditions in migraine patients [1, 4–6]. Overuse of symptomatic drugs is regarded as one of the most important risk factor for the transformation of episodic migraine into CM and drug-seeking tendency due to fear of headache in chronic migraine patients shares with OCD, the compulsive quality of the behavior [6]. The presence of obsessive–compulsive symptoms in migraine patients is an unfortunately often underestimated issue. Anticipatory anxiety due to fearing of headache onset with social and professional impairment is the most important aspect that causes the compulsive compounds-taking behavior and psychological symptomatic medications dependence. Aim of this study was to review the clinical history of a sample of CM patients with MO in which an obsessive–compulsive trait was identified, performing a comparison with a sample of patients without obsessive–compulsive trait: this

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retrospective study was designed into investigate if there was a difference in response to prophylaxis treatments and relapse after overuse medication withdrawal between the two groups.

Patients and methods

We selected 14 patients with positivity to Spectrum Project OBS (obsessive–compulsive disorder) questionnaire [7, 8] and other 14 patients with negativity to the same tool from among a sample of patients who were enrolled in a previous study [1] on the psychopathological profile of patients suffering from CM with MO [9]. All the 28 patients underwent at least one inpatient withdrawal program to stop MO in our Headache Center, and we could obtain a detailed clinical history of the past 5 years, as far as prophylaxis treatments, clinical response and withdrawal programs in other Headache Centers. Data obtained in the two study groups were compared in terms on numerical findings.

Results

According to data obtained from the clinical records referring to the previous 5 years, patients with OBS-questionnaire positivity showed a worse clinical course and a tendency to early relapse in MO after symptomatic medication withdrawal. Compared to those without obsessive–compulsive trait, patients with obsessive–compulsive trait at Spectrum Project OBS questionnaire had used a higher number of prophylaxis treatments (mean 5 treatments, range 3–11 vs. mean 3, range 1–6, respectively) and reported a higher number of relapses to MO (mean 3, range 2–7 vs. mean 2, range 1–4, respectively). They also had an earlier re-admission to inpatient withdrawal program (mean 8 months after previous withdrawal program, range 6–15 months in obsessive–compulsive patients vs. mean 15 months, range 13–25 in those without obsessive–compulsive trait, respectively) and a more evident tendency to use many different symptomatic compounds to treat their migraine attacks. Furthermore, patients with obsessive–compulsive trait showed a worse response to standard compounds for migraine prophylaxis than to drugs which are primarily indicated for treating psychiatric disorders (tricyclics, SSRIs, SNRIs, trazodone, benzodiazepines, mood stabilizers or antipsychotics).

Discussion

The psychopathological profile may have a prognostic significance in patients with CM [10]. A significant association between CM with MO and psychiatric disorders has been demonstrated, but the link between this disabling headache form and OCD or obsessive–compulsive trait is actually not well defined. A subclinical OCD and the compulsive quality of patient's behavior can represent a major risk for MO in migraine patients [6], and its presence may influence the clinical course of migraine, leading to failure of standard migraine preventive treatments. The behavior OCD and MM with MO patients may share several aspects. Previous reports about personality in CM patients highlighted that the drug-seeking tendency due to fear of headache onset in migraine patients is similar to compulsive behavior in OCD patients [1, 6]. Although results were obtained in patients not suffering from OCD but with obsessive–compulsive trait, the results obtained in a previous retrospective study [6] indicate this psychopatological aspect as a possible predictive factor for refractoriness to treatments in CM, and as a risk factor for the maintenance of MO. We note that subclinical OCD and obsessive–compulsive trait in migraine patients might be often underdiagnosed and thus undertreated, with the potential of promoting the switch from episodic migraine to CM and/or to MO.

In conclusion, our results show that the comorbidity of OCD should be always evaluated in patients with CM and MO as it may play a relevant role—particularly if not treated—among the risk factors favoring the progression of episodic migraine to the chronic form, and/or the tendency to a pathological behavior that prompts the overuse of symptomatic medications.

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

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POSTERS

Chronic cluster-like headache secondary to prolactinoma responsive to cabergoline: a case report and review of the literature

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Introduction: Chronic cluster-like headache was seldom reported in association with prolactinoma [1]. We report a case of cluster headache in a patient with prolactinoma, responding dramatically to cabergoline.
Case history: A 61 year-old man experienced, since the age of 45 years, nocturnal attacks of severe, right orbital and frontal pain, lasting 60–180 min and occurring once a day. The attacks were associated with ipsilateral conjunctival injection, lacrimation, nasal congestion and rhinorrhoea. Cluster periods usually lasted 15–40 days, with remission periods of months. Since the age of 59 years, the attacks' frequency progressively increased to one or more episodes per day, without any temporal pattern, with remission periods lasting less than 15 days. Verapamil, methysergide, topiramate and valproate were ineffective. 1.5 T brain magnetic resonance imaging (MRI) was normal. For the persistence of pain, a 3 T brain MRI was performed, showing a right-side adenoma. Prolactine level was 469.4 ng/mL. The patient was given cabergoline 0.5 mg on alternate day, with complete remission of pain after 2 months.
Conclusion: Few cases of cluster-like headache with pituitary adenomas have been reported [2], and six of them were associated with prolactinoma. Symptomatic cluster headache should be suspected when the clinical features of headache are atypical (absence of the typical periodicity or duration, a persistent headache between attacks, poor response to recognized treatments and the presence of atypical neurological signs or symptoms). Dopaminergic drugs, as cabergoline, may improve or exacerbate headache; this observation is probably related to a complex interaction of the physical effects of the tumor and the central action of dopamine agonists.

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Inpatient withdrawal treatment for chronic migraine with medication overuse and follow-up

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Objective: To investigate a group of CM with medication overuse patients before and after inpatient withdrawal pharmacological program and after a long-term follow-up.
Methods: We hospitalized 114 CM patients with medication overuse (11M, 103F, mean age 48.6 ± 14.5) at our Headache and Pain Unit for 15 days and re-contacted them after discharging. We collected data at baseline (T0) and followed-up after 3 (T3), 6 (T6), 12 (T12), 18 (T18), 24 (T24), 36 (T36), 48 months (T48). Inpatients were treated by discontinuation of the overused drugs and with a therapeutic protocol including i. v. dexamethasone, hydratation, anxiolytic and antidepressant therapy. Patients started prophylactic drugs and underwent to psychological and behavioural therapy to identify triggers and promote healthy life style. Once a day cranium-sacral and hydrokinesis therapy was applied as coadjuvant approach. Migraine disability was assessed by MIDAS, depression with Beck Depression Inventory (BDI) and anxiety with State Trait Anxiety Inventory (STAI-1, STAI-2) questionnaires. Quality of life was assessed using Short Form-36 Healthy Survey (SF-36).
Results: A comparison of MIDAS total scores between baseline (120.2 ± 71.5) and other timelines showed a significant reduction at T3 (56.5 ± 59.9 $p < 0.001$) and it was not lost at the others timelines of follow-up (T6: 56.4 ± 60.9 $p < 0.001$; T12: 61.9 ± 68.8, $p < 0.001$; T18: 71.2 ± 64.8, $p < 0.002$; T24: 65.6 ± 64.8 $p < 0.001$; T36: 63.5 ± 64.3 $p < 0.001$; T 48: 72 ± 64.9 $p < 0.002$). Days of headache were T0: 63.2 ± 25.7; T3: 28.1 ± 24.3 ($p < 0.001$); T6: 26 ± 22.6 ($p < 0.001$); T12: 28.1 ±23.1 ($p < 0.001$); T18 30.7 ± 25.9 ($p < 0.001$); T24: 30.5 ± 23.5 ($p < 0.001$); T36 38.5 ± 31.7 ($p < 0.001$); T48:41.7 ± 33.4 ($p < 0.002$). STAI 1 score did not differ at any time, STAI-2 and BDI scores significantly reduced at T3 and maintained the increment at other times. Physical pain, social activity and mental health of SF-36 significantly improved at any timelines of follow-up.
Conclusions: Different factors can contribute to the development and perpetuation of medication overuse in chronic migraine. Withdrawal in hospital setting is considered the first step for helping these patients to stop medication overuse.

Triptans in migraine therapy: incomplete revolution?

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The evaluating patterns of specific acute migraine treatment obtained through the analysis of prescriptions in the population is a main step towards assessing the quality of migraine care. Data from many countries shows today a very low percentage of migraine patients treated with triptans and a low frequency of utilization. We have reviewed data on triptan turnover, that is the percentage of those starting triptans and of those who interrupt triptan treatment. A high percentage of new users (over 50 %) and lapsed users (40–50 %) was reported [Table]. A lower percentage of discontinuation (25–28 %) was found in some studies, but these include only subjects with a long history of migraine or with severe migraine. Confirming previous data, a recent large US study shows that in new triptan users discontinuing the index triptan, only a small percentage (7.4 %) switched to a different triptan, while 67 % switched to a non triptan medication. A better management of migraine in primary can ameliorate the use of triptans in migraine treatment. Until now, however, the so called "triptan revolution" initiated with sumatriptan development remains to be completed.

Study	Triptan users (no)	Study period (months)	%
New users			
Biagi (2011)	34,915	12	48
Panconesi (2010)	1,022	12	52
Lugardon (2007)	13,860	6	63
Sondergaard (2006)	2,463	3	25
Etemad (2005)	8,488	12	63
Lapsed users			
Katic (2011)	40,892	24	46
Golden (2010)	6,625	24	54
Panconesi (2010)	921	12	46
Etemad (2005)	5,294	12	39
Savani (2004)	3,196	15	55
Cady (2009)	785	12	25
Bigal (2010)	1,392	12	28

Chronic headache and body mass index: a case–control study

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Introduction and aim: In recent years clinical research has focused on the possible role played by obesity as a risk factor for headache chronification. The aim of this case–control, hospital-based study was to evaluate: the prevalence of overweight and obesity in subjects with chronic migraine (CM) and chronic tension-type headache (CTTH); and the possible correlations between body mass index (BMI) and both headache types.
Materials and methods: We studied 79 patients, 46 with CM and 33 with CTTH, consecutively referred to the Adult Headache Centre of the University of Palermo (A.H. Study) between 2007 and 2009, and 316 controls without headache (each patient was matched by sex and age to four controls).The headache diagnosis was established according to the ICHD-II criteria. BMI classes were defined according to WHO guidelines.
Results: Mean age was 47.6 years (±17.8 years) for the 79 patients with chronic headache (66 F, 13 M) and 47.6 years (±17.8 years) for the 316 controls (264 F, 52 M). The BMI status did not differ between groups (mean BMI was 27.7 ± 4.8 in chronic headache patients and 27.3 ± 5.1 in controls). In the chronic headache group, 32.9 % were obese, 40.5 % pre-obese and 26.6 % overweight. In the control group, 26.0 % were obese, 40.3 % pre-obese and 33.7 % overweight. Following multiple logistic regression analysis, the presence of obesity and pre-obesity was not associated with chronic headache (obesity: OR = 1.4, 95 % CI 0.7–2.9; pre-obesity: OR = 1.6, 95 % CI 0.5–2.2).
Conclusion: Our data suggest that BMI abnormalities are not associated with CDH. However, considering previous reports of an association of obesity and migraine in population-based studies, we cannot exclude a selection bias.

Anxiety disorder, depression and chronic daily headache: a case–control study

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Introduction and aim: Chronic headache cause high disability in sufferers and high social cost. Data regarding possible comorbid diseases, manly depression and anxiety, are still few and conflicting. The aim of this case–control, hospital-based study was: to evaluate the prevalence of depression and anxiety in subjects with chronic migraine (CM) and chronic tension-type headache (CTTH); and to compare the results with those found in a control group without headache.
Materials and methods: We studied 79 patients, 46 with CM and 33 with CTTH, consecutively referred to the Adult Headache Centre of the University of Palermo (A.H. Study) between 2007 and 2009, and 316 controls without headache (each patient was matched by sex and age to four controls).The headache diagnosis was established according to the ICHD-II criteria. Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HAD).
Results: Mean age was 47.6 years (±17.8 years) for the 79 patients with chronic headache (66 F, 13 M) and 47.6 years (±17.8 years) for the 316 controls (264 F, 52 M). The mean HAD-D score was 8.6 ± 4.3 in the chronic headache group and 7.0 ± 3.5 in the control group; (p = 0.00). The mean HAD-A score was 11.2 ± 4.5 in the chronic headache group versus 9.0 ± 3.7 in the control group. Following multiple logistic regression analysis, the presence of depression and anxiety was associated with chronic headache

(depression: OR = 2.2, 95 % CI 1.2–4.1; anxiety: OR = 2.4, 95 % CI 1.3–4.3).
Conclusion: According to our data, anxiety and depressive symptoms are more prevalent in chronic headache, and correlate to an increased risk of chronic headache.

Nutraceutical administration in childhood migraine prophylaxis: effect on disability

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Background: In developmental age migraine is a very common neurological disorder, but very few drugs are disposable.
Aim of study is comparing the middle term effect of two nutraceutical complexes on frequency, disability grade and intensity of migraine in a paediatric sample.
Materials and methods: One complex composed by Ginkgolide B/Coenzyme Q10/Riboflavin/Magnesium (complex A) was oral administered as prophylactic therapy twice a day for 6 months to 187 school-aged patients and other one composed by the association of L-tryptophan/5hydrossitriptophan (*Griffonia simplicifolia*)/vitamin PP/vitamin B6 (complex B) to other 187 children with MoA, matched for age ($p = 0.575$) and sex distribution ($p = 0.918$). Each patient kept a journal to record: number and intensity of attacks and concomitant symptoms. To assess the intensity, disability grade and behavioural variations linked to migraine a visual analogue scale (VAS), the PedMIDAS scale and a behavioural scale were administered at the beginning and at the end of treatment.
Results: Our results show that the two nutraceutical complexes can reduce all the disabilities aspects of migraine in our samples and the effects of Complex A after 6 months of treatment seem to have more efficacy than Complex B ((Delta% frequency $p < 0.001$, Delta% duration $p < 0.001$, Delta% PedMIDAS $p < 0.001$, Delta% VAS $p \leq 0.001$), also for the behavioural aspects (Delta% Behaviour $p \leq 0.001$,) that are very important for the dynamics within the family of migraineurs patients, suggesting its improved therapeutic effect in the middle-long term.
Conclusion: Our findings also suggest that in childhood headache management, the use of alternative treatments could be considered as soft therapy without adverse reactions even in the middle-long term treatment.

Pregnancy after a cryptogenic stroke in migraine sufferers. Outcome in four cases

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Stroke tends to be a catastrophic event at whichever age it occurs, but this is especially true, albeit rare, in young adults, particularly pregnant women, as both the mother and the foetus could suffer the consequences. Most young strokes are eventually ascribed to so-called cryptogenic stroke (CS), i.e., no identifiable cause can be found even after extensive examination. There does, however, appear to be an association with a history of migraine; indeed, the risk of ischaemic stroke is doubled in migraine with aura (MwA), but not in migraine without aura (MwoA) sufferers [1]. Furthermore, the presence of patent foramen ovale, frequently associated with MwA, as well as smoking and oral contraceptive use increases the risk of stroke, as well as that of recurrence in pregnancy and puerperium, two well-documented pre-thrombotic conditions [2]. This raises the issue of what kind of thromboprophylaxis strategy to adopt, if any. Unfortunately, however, available data pertaining to prevention of stroke in pregnant women at risk of recurrence is scarce, and evidence of the efficacy and safety of antithrombotic treatment during pregnancy has not yet been well established [3].
We report four cases of women with a history of both CS and migraine (two MwoA and two MwoA and MwA), who undertook a planned pregnancy. No adverse maternal and foetal events were registered during either pregnancy, caesarean delivery or puerperium in the three patients treated with antithrombotic agents, while a minor stroke occurred at the 28th week in the untreated patient. In our experience, pregnancy and delivery in patients with a history of CS are safe if treated with anti-thrombotic agents throughout gestation and soon as possible post-partum. Therefore, a previous history of CS should not be considered an absolute contraindication for pregnancy in young adult women with an associated history of migraine.

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Stroke risk factors in migraine sufferers. Results of the ERICe study

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Although migraine is one of the most common and disabling neurological disorders in western countries (1), and has been recently reported (2) as an independent stroke risk factor, it still remains widely under-diagnosed and under-treated (3). Thus the objective of the present survey was to assess the prevalence of migraine and cardiovascular factors risk in a sample of residents of the Aosta municipality. A structured questionnaire was therefore mailed to 850 female and 860 male 20–54 year-old residents representative of the study area population, as part of the ERICe project, an information campaign promoted by the regional Association against Stroke (ALICe). The ultimate aim of the campaign was to increase awareness of stroke risk in the local general population and migraine, but herein we focus on the prevalence of cardiovascular risk factors in the migraineurs. *Results* Of the 387 respondents, a total of 144 (37.2 %) reported suffering some form of headache, and according to the ICHD-II criteria (4), 18 % (70/387) were diagnosed with migraine. The prevalence of stroke risk factors in the migraine group was: hypertension 7.2 %, diabetes mellitus 0 %, smoking 31 %, oral contraceptive use 3.6 %, alcohol use 36 %, low fruit and vegetable consumption 28 % and obesity 22 %. No significant differences were found in any of these factors, except for current smoking in migraineurs ($p < 0.001$) and hypertension ($p < 0.05$) in headache sufferers. *Conclusion* Although the study was undoubtedly limited by a small sample population and non-response bias, it did reveal associations

between stroke risk factors and migraine/headaches. Although this association was fairly weak, considering the worldwide prevalence of the conditions in question, it does merit assessment on a larger scale. Indeed, a larger study is already being planned; should it confirm the present findings, it will highlight the need not only to identify headache and migraine sufferers in general, but also to assess known patients for stroke risk factors, particularly in migraine with aura. Indeed, if our results are borne out, it may well ultimately transpire that treating the former conditions has the potential to prevent or at least reduce the risk of the latter in a significant number of people.

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Clinical presentation, course, neuroimaging findings and response to treatment in three suspected cases of Tolosa-Hunt syndrome

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Tolosa-Hunt syndrome (THS) is a rare cranial neuralgia caused by idiopathic inflammation of, generally one but occasionally both, cavernous sinuses and less frequently the superior orbital fissure and/or orbital apex. Although THS usually resolves either spontaneously or after treatment, it can persist or relapse and remit in some cases.

The four IHS criteria (1) describe the course and features of THS as: "episode(s) of unilateral orbital pain for an average of 8 weeks if left untreated; association with paralysis of one or more of the third, fourth, and/or sixth cranial nerves, which may coincide with onset of pain or follow it by a period of up to 2 weeks; pain is relieved within 72 h of steroid therapy initiation; and exclusion of other conditions by neuroimaging and (not compulsory) angiography". In this context, magnetic resonance imaging (MRI) without contrast agents can reveal enlargement of the cavernous sinus, narrowing of the intracranial internal carotid artery and/or infiltration of orbital structures by abnormal tissue, which appears isointense with grey matter in T1, and isohypointense in T2-weighted images, and whose signal intensity markedly increases after contrast injection (2). These findings, if present, are typical of THS but not specific, as they can also be found in other progressive intracranial diseases such as neoplasms and inflammatory conditions. Herein we report three cases, two females and one male, recently examined due to unilateral painful ophthalmoparesis (and associated reduction in visual acuity in one case) similar to that described for THS.

MRI and CT scan showed findings typical of THS in two cases. One patient experienced progressive spontaneous remission of the pain and partial ophthalmoparesis. The other two cases were both treated with oral prednisone, resulting in complete cessation of pain, in one case very rapidly, but only partial resolution of the ophthalmoparesis.

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Medical conditions associated to chronic daily headache: SPARTACUS sub-study

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Background: Chronic daily headache (CDH) is defined as headache occurring $\geq$15 days per month for at least 3 month. Many medical conditions have been reported to be associated with CDH. To date, there are no population based studies in Italy.

Objectives: To identify medical conditions associated with development of medication overuse in chronic headache sufferers.

Methods: 435 of the 636 CDH sufferers identified using a validated questionnaire in the SPARTACUS-study population, underwent a semi-structured interview by their GPs about current and past associated medical conditions. Patients were divided into two diagnostic groups: CDH with medication overuse ($n = 127$, mean age 49 ± 14) and CDH without medication overuse ($n = 308$, mean age 53 ± 17). We use descriptive statistics and Chi-square test.

Results: CDH patients complained cardiovascular (31.5 %), gastrointestinal (20.5 %), respiratory (10.3 %), thyroid (14.5 %), immunological (6.2 %), musculoskeletal (23.2 %), neurological (5.5 %), psychiatric (20 %), genitourinary (6.2 %), other (5.3 %) diseases and trauma history (3.2 %). Comparing CDH patients with and without medication overuse, we observed significant difference only concerning cardiovascular disease prevalence (22.8 % vs 35.1 %, $P = 0.017$). In particular, patients with CDH without medication overuse showed a high prevalence of hypertension with respect to those with medication overuse (28.6 % vs 17.3 %, $P = 0.019$).

Conclusions: Our study revealed an high prevalence of medical disease among CDH patients. Unexpectedly hypertension, and cardiovascular diseases in general, are more frequent in CDH without medication overuse, probably due to the older age of non-overusers.

Treatment of withdrawal headache in patients with medication overuse headache (MOH): a randomized, single-blinded, placebo controlled study

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Introduction: Withdrawal headache in MOH is a therapeutic challenge.

Objectives: we performed a randomized, single-blinded, placebo controlled trial for the evaluation of the efficacy of methylprednisolone or paracetamol in the treatment of withdrawal headache in patients with MOH.

Materials and methods: MOH patients, unresponsive to the prophylaxis in the run-in period, underwent withdrawal therapy on an in-patient basis. Overused medications were suddenly stopped and methylprednisolone 500 mg i. v. (A) or paracetamol 4 g i. v. (B) or placebo i. v. (C) were given daily for 5 days. Severity of headache

and of autonomic symptoms was reported in a daily diary. Metoclopramide and/or lorazepam were allowed as rescue medications.
Chi-square test and Student's *t* test were used.
Results: 38 consecutive patients (34 F, 4 M; mean age 44.7 ± 9.1) were enrolled: 13 in A, 15 patients in B and 10 in C. Overused medications included triptans (50 %), simple analgesics (5.3 %), combination analgesics (7.9 %); 42.1 % of patients overused two or more drugs' categories. No differences about the overused drugs, the time of overuse, the days of headache and the days of overuse per month were found. Withdrawal headache on the 5th day was absent in 2 patients (15.4 %) of A, in 3 patients (20 %) of B and none of C ($p \geq 0.5$). 2 patients of C dropped on the 2nd day of withdrawal. Mean headache intensity was significantly lower in A and B versus C on the 1st day ($p \leq 0.04$), and in A versus C on the 2nd day (p 0.007) of withdrawal. The three groups did not show differences about the mean number of days with autonomic symptoms. The mean intensity of autonomic symptoms was significantly lower in A and B versus C on the 1st day of withdrawal ($p < 0.0009$). The mean number of rescue medications taken during the 5 days of withdrawal was significantly lower in the A (3.5 ± 2.2) and B (2.1 ± 1.5) versus C (7.7 ± 5.7; $p \leq 0.02$).
Conclusion: our preliminary data suggest that methylprednisolone and paracetamol are superior to placebo in reducing the intensity of rebound headache and of autonomic symptoms on the first day of withdrawal, and in reducing the consumption of rescue drugs in MOH patients. Methylprednisolone resulted superior to placebo in reducing headache intensity also on the 2nd day of withdrawal.

PACE study: past-year prevalence of tension-type headache in Parma's adult general population

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Introduction: Primary headache prevalence and features in the Italian general population have been little studied so far. The PACE study (PArma CEfalea, or "Headache in Parma") is an observational study aimed at detecting the prevalence and clinical features of primary headaches in the city of Parma's adult general population.
Objectives: To evaluate in a sample representative of Parma's adult general population the past-year prevalence of (a) infrequent, (b) frequent, and (c) chronic tension type headache (TTH).
Materials and methods: The initial study sample (n = 1,270) consisted of all residents registered with a general practitioner (LB) in downtown Parma. The study population can be considered representative of the Italian adult general population for age/gender distribution. Using a specially developed, previously validated 13-section questionnaire, four physicians of the Parma Headache Centre administered face-to-face interviews to 904 responders (71.2 % of the sample) aged ≥18 years between September 2007 and February 2009. The responders included 508 women (56.2 %; mean age 55.9 years, SD 17.2 years, max. 92 years) and 396 men (43.8 %; mean age 55.0 years, SD 18.2 years, max. 91 years). Headache diagnosis was made according to the International Classification of Headache Disorders 2nd Edition (ICHD-II).
Results: A total of 175 subjects (19.4 %, 95 %CI 16.8–21.9) had a diagnosis of TTH, 20.1 % women (95 %CI 16.6–23.6) and 18.4 % men (95 %CI 14.6–22.3), the F:M ratio being 1.1:1. The subjects who suffered from TTH were distributed as follows: (a) 81 subjects (9 %, 95 %CI 7.1–10.8) had infrequent TTH, including 45 women (8.9 %, 95 %CI 6.4–11.3) and 36 men (9.1 %, 95 %CI 6.3–11.9). (b) A diagnosis of frequent TTH was made in 89 subjects (9.8 %, 95 %CI 7.9–11.8); 54 women (10.6 %, 95 %CI 7.9–13.3) and 35 men (8.8 %, 95 %CI 6–11.6). (c) The crude prevalence of chronic TTH was 0.6 %, 95 %CI 0.1–1 (F 0.6 %, 95 %CI 0–1.3; M 0.5 %, 95 %CI 0–1.2).
Conclusion: Our study results indicate past-year prevalence of TTH that are lower than those found in the epidemiological population-based studies in Western countries. No differences are observed in sex distribution.

"Headache frequency and characteristics in chronic cocaine users: a cross sectional study"

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Background: The association between headache and cocaine use has been investigated only with retrospective studies so far.
Aims: (1) to evaluate the prevalence of headache and its characteristics in chronic cocaine users in a cross sectional study. (2) to assess any temporal correlation between the onset of cocaine use and the onset of headache.
Methods: Cross sectional study on consecutive subjects with chronic cocaine use attending a Drug Addiction Service from 1/8/10 to 31/12/11. Subjects were visited and interviewed by a psychiatrist (VO) who gathered detailed information on cocaine use, concomitant psychiatric disorders/treatments and other comorbidities, and by a neurologist (LF) who assessed the presence of lifetime headache and/or current headache and gathered information on headache characteristics and its correlation cocaine use. Subjects were divided in 3 groups: no headache (group 0), current headache and positive history of pre-existing headache (group 1) and current "de novo" headache (individuals who developed headache after the onset of cocaine use) (group 2).
Results: Eighty subjects (mean age 37.8 ± 9.4; 16 F:64 M) were enrolled. Seventy-two (90 %) had current headache. Of these, 29 (40.2 %) had a pre-existing history of headache [MWOA = 15, probable MWOA = 6, TTH = 4, CM = 2, other = 2, while 43 (59.7 %) developed "de novo" headache following the onset of cocaine use [cocaine-induced headache = 2, MWOA = 17, probable MWOA = 8, TTH = 9, CM = 1, other = 6]). Seven subjects had medication overuse (4 in group 1 and 3 in group 2).
There were no differences between the 3 groups as regards socio-demographic characteristics.
Group 1 patients showed a longer duration of headache history ($p = 0.002$), more severe headache intensity ($p = 0.001$) and nausea ($p = 0.041$) during the attack and more frequent analgesics assumption ($p = 0.04$) compared to group 2 (one-way ANOVA analysis). Group 2 patients revealed a better response to analgesics than group 1 ($p = 0.047$) (one-way ANOVA analysis).
In group 2, Pearson's analysis evidenced a linear correlation between the age of headache onset and the age of first use of cocaine ($p = 0.008$, $r = 0.401$) and between the age of headache onset and the age of continuous use of cocaine ($p = 0.016$, $r = 0.367$). A multiple regression analysis showed that the age of

headache onset was predicted in the group 2 by the age of first use of cocaine and the age of continuous cocaine use with a value of R^2 of 18 %.
Discussion and conclusions: Headache is extremely frequent (90 %) but cocaine-induced headache (ICHD-II: 8.1.66) is extremely rare (2.5 %) in chronic cocaine users. Migraine without aura and probable migraine without aura were the most frequent types of headache in both group. Almost 60 % of chronic cocaine users develops headache after the onset of cocaine use. The combination of cocaine with cannabis or alcohol does not influence the presence and characteristics of headache. Usually, headache starts >2 h following cocaine use. Headache onset shows a linear correlation with duration of cocaine use, but is not correlated to the doses, ways of assumption and frequency of cocaine use. In the de novo headache group (group 2), the age of headache onset could be predicted by the age of first use of cocaine and the age of continuous use of cocaine.

The sporadic hemiplegic migraine (SHM) pathogenesis: the role of SCN1A gene

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Sporadic Hemiplegic Migraine (SHM), whose etiology is still unknown, is a paroxysmal disorder characterized by motor aura and headache. Three studies of SHM patients demonstrated CACNA1A mutations essentially in patients with cerebellar signs, permanent cerebellar ataxia or cerebellar atrophy on CT scan. In 2008 Thomsen studied 105 SHM patients, without permanent signs, and the found mutations were only in CACNA1A and ATP1A2 genes. Moreover, two authors confirmed the absence of mutations in SCN1A gene in all the screened SHM patients. Results from genetic and functional studies indicate that neuronal hyperexcitability has a pivotal role in the pathogenesis of hemiplegic migraine and multimodal neuroimaging (MRI, DWI, MRS, SPET) in prolonged attacks supports evidence for a primary neuronal dysfunction. In this review we have focalized the pathogenesis of the sporadic form and we have tried to understand if the absence of mutations in SCN1A gene suggests that SHM is a distinct form from FHM.

Botulinum A toxin for treatment of chronic migraine

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Introduction: Chronic migraine is a common and debilitating headache syndrome. Botulinum neurotoxin (BoNT), a potent toxin produced by the anaerobic bacterium clostridium botulinum, used largely for treatment of disorders associated with increased muscle tone and hyperidrosis, has been recently used for patients suffering from chronic migraine.
Aim: As the significant population of chronic migraine patients, refractory to common therapeutic prophylaxis, BoNT has been used in our clinical experience for treating patients referring to our headache centre and suffering from chronic migraine with medication overuse.
Method: Ten patients have been submitted to a withdrawal treatment from medications in a day hospital setting and after that, they have been treated by BoNT A injection in multiple sites according to the protocol of the PREEMPT study at the dosage of 150 U for 31 sites. Every session of local injection (150 U per 31 sites) has been repeated every 3 months for a period of almost 1 year. The clinical indexes were recorded by using an headache daily diary, with the number of medication intake per month and the days of headache per month. MIDAS questionnaire was given for recording the disability levels pre and during treatment period.
Patients were followed for 1 year.
Results: Days of headache/month decreased during the period of treatment (pre 21.4 + 7.9 post 13.8 + 10.9 $p < 0.01$). Also medication intake decreased (pre 19.6 + 8 post 11.7 + 9.5 $p < 0.01$).
At the same time the disability level decreased as evidenced from the MIDAS total score (pre 86.7 $\pm$ 73 post 74.9 + 91.1)
Discussion: Although these results are preliminary they led to intense efforts to evaluate the analgesic properties of BoNT A and to assess their clinical applicability.
The pharmacological profile of BoNT A makes it a good candidate for migraine prevention. Its long duration of action (3 months) makes it particularly attractive for patients who are not compliant with the daily use of preventive medications, or if they cannot tolerate it or when they are refractory to preventive medications.

Day hospital withdrawal for chronic migraine with medication overuse: results at 3 years follow-up

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Background: patients with chronic headache and medication overuse are particularly difficult to treat, with no one approach being universally accepted. Some type of withdrawal program, however, is typically implemented before beginning a pharmacological prophylaxis treatment. Different withdrawal modalities have been performed for managing these patients: at first step, in-patient withdrawal has been confirmed effective in preceding clinical experiences. In recent years new modalities for withdrawal have been developed as day-hospital setting withdrawal.
Objective: Purpose of this study was to determine the clinical course of a sample of chronic migraine patients with medication overuse 3 years after day hospital withdrawal.
Methods: A group of 202 patients were treated. Patients were suffering from chronic migraine with medication overuse according with HIS criteria. All patients were submitted to a day hospital withdrawal and then they were followed with meetings every 3 months until the first year and then every 6 months until the last follow-up 3 years after withdrawal.
Results: Eighty patients achieved the last follow-up meeting 3 years after withdrawal. Patients clinically improved: days of headache per month decreased significantly from 22.8 (SD 5.8), at baseline to 7.8 (SD 4.9); consumption of medications per month decreased significantly too from 26.7 (SD 19.9) to 7.4 (SD 5.0) at the last follow-up.
Conclusions: From these results the day hospital setting for withdrawal, followed by periodic clinical meetings, seems to be effective for this category of patients to improve significantly at long-term headache frequency and analgesics intake.

Abnormalities of immune parameters in chronic migraine with medication overuse

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Background: It has been postulated in the past that migraine and chronic forms in particular, has been connected to immunologic disturbances. Moreover the psychiatric comorbidity is often responsible of chronification of migraine but also of developing of particular immune function alterations.
Aim: Of our study was to evaluate 2 groups of subjects: first group of patients suffering from chronic migraine with medication overuse before a withdrawal procedure; second group control subjects of same age and general characteristics. Blood samples were collected form both of groups
Methods: Peripheral Blood samples from 25 patients suffering from chronic migraine with medication overuse and 25 controls were collected. Samples were collected in the morning, and the following analysis were performed: lymphocytes and subsets, CD3, CD4, CD8, CD 19, T reg.
Patients were also submitted to the MIDAS questionnaire for evaluating the disability level induced from their headache status
Patients were studied before an intervention of withdrawal in a day hospital setting.
Results: From the analysis of samples we obtained the following results: CD4 were significantly higher in patients than in controls ($1{,}102.24 \pm 464.28$ vs. 790.52 ± 206.11 $p < 0.007$). CD19 increased significantly too in patients (385.68 ± 175.89 vs. 193.72 ± 72.07 $P < 2.46E{-}06$); also CD8 and CD 3 increased significantly in patients than in controls (respectively CD8: 747.93 ± 271.09 $p < 0.0006$; CD3 1949.42 ± 642.08 vs. 1356.62 ± 288.1 $p < 0.0001$).
Other analysis did not show any significant abnormality.
Discussion: The alterations reported, although limited to particular parameters, may indicate a inflammatory state in patients suffering from chronic form of migraine with medication overuse, similar to those showed from preceding literature.
More studies will be necessary to confirm these preliminary results and to explain the clinical implications of these abnormalities.

Occipital nerve stimulation in the treatment of chronic medically intractable SUNCT and SUNA syndromes: a long term follow-up study in nine patients

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Objective: To report on the outcome and follow-up of nine chronic medically intractable SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing) and SUNA (Short-lasting Unilateral headache attacks with Autonomics symptoms) patients treated with occipital nerve stimulation (ONS).
Background: SUNCT and SUNA are primary headaches characterized by repeated attacks of very severe headaches in association with cranial autonomic features that usually occur several times daily. They can be medically intractable, in which case neurally destructive or cranially invasive treatments can be offered. ONS offers a non-destructive and relatively low-risk surgical alternative.
Methods: Nine medically intractable patients (6 SUNCT, 3 SUNA) had bilateral ONS implants. Data was collected retrospectively for demographics, diagnosis and previous treatments. Data about frequency, intensity and duration of attacks were collected from headache diaries at baseline and after the implant, to assess the objective improvement of the headache. Disability, anxiety and depression scales were administered at baseline and during the follow-up.
Results: At a median follow-up of 31 months (range 16–48 months), all but one patient showed substantial improvements: four patients became pain free, two, almost pain free ($\geq$95 % improvement), and two had a remarkable reduction in attack frequency and severity ($\geq$80 % improvement). Five patients were able to discontinue preventive medications, whereas two, to reduce them. After a rapid initial improvement, the maximum benefits of ONS were attained over few months. Battery failure or voluntary stimulator switch-off were followed by recurrence or worsening of the attacks within few days in most of patients. Adverse events included new-onset hemicrania continua, lead migration, exposition of the electrode and muscle pain over the leads.
Conclusion: ONS seems to be an effective and safe treatment for medically intractable SUNCT and SUNA syndromes. Given the poor and controversial results on the surgical management of these conditions, ONS might be considered the surgical treatment of choice for medically intractable SUNCT and SUNA.

Impact of migraine and chronic migraine on disability and reduced productivity: a cross-sectional study

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Migraine is a common disease that, in association with specific lifestyle and life events, may undergo a chronification process, often associated to medication overuse. Chronic Migraine with Medication Overuse (CM-MO) is a condition characterised by more frequent attacks that are likely to impact on patients' disability and productivity, with relevant consequences in terms of disease cost (445€/year/patient for migraine; 1,875€ for CM-MO). Aim of this paper is to assess differences between patients with episodic and chronic migraine with regard to disability and reduced productivity.
Patients with migraine (MIG) and CM-MO in the productive age and employed, were consecutively enrolled and administered the MIDAS and the WHO-DAS-2. Independent-sample t test was performed to assess group differences; $P < 0.05$ was set for statistical significance. In total, 178 patients were enrolled (80 with MIG, 98 with CM-MO; 144 females), with no group differences for age (40.9 for MIG; 41.4 for CM-MO), years of formal education and number of worked hours per week. Significant differences were instead found at MIDAS (25.3, 95 % CI 20.3–30.4 for MIG; 85.5, 95 % CI 71.9–99.1 for CM-MO) and WHO-DAS-2 global disability (20.1, 95 % C.I. 16.9–23.3 for MIG; 29.4, 95 % CI 26.8–32.0 for CM-MO). Considering the items related to difficulties with remunerative job, significant differences were found too, both in terms of number of workdays lost (1.8, 95 % CI 1.2–2.5 for MIG; 4.1, 95 % CI 2.8–5.3 for CM-MO), and in terms of difficulties in dealing with work duties as measured with

WHO-DAS-2 Work/school activities scale (28.9, 95 % CI 24.4–33.4 for MIG; 35.6, 95 % CI 31.1–40.0 for CM-MO).
Recent estimates show that the cost of CM-MO is approximately four times higher: the difference is relevant for direct healthcare costs (86€ for MIG; 267€ for CM-MO) and even more for indirect costs (359€ for MIG; 1,608 for CM-MO). Our results are consistent with the cost estimate and we recommend that longitudinal studies be performed to assess the effectiveness of treatment not only for reducing headaches frequency and intensity, but also to reduce disability and increase patients ability to be productive in the workplace.

Search for possible predictive factors of the course of migraine without aura during pregnancy

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As is known from the literature, attacks of migraine without aura (MO) are generally reduced and sometimes even disappear altogether during pregnancy. Unfortunately, however, in a minority of cases this improvement will not occur.
In order to evaluate the possible existence of clinical features that can predict the course of MO during pregnancy, we reviewed the clinical records of 121 MO patients seen on a consecutive basis at the University of Parma Headache Centre who had at least one pregnancy after their MO onset.
The women were divided into two groups: Group A with 94 patients showing a favourable MO evolution, and Group B with 30 patients showing an unfavourable MO evolution.
The two groups were compared using statistical tests (Student's t test, Wilcoxon-Mann–Whitney test, Chi-square test, Fisher's test) to evaluate the following aspects: age at MO onset; family history of migraine; age at menarche and possibly menarche-related MO onset; evolution of attacks related to menstruation and the possible use of oral contraceptive; pain site; associated symptoms; unhealthy personal habits; and possible MO association with migraine with aura and/or tension-type headache.
Statistical significant differences were found between the two groups in the predominant pain site and in the MO association with tension-type headache: pain was less consistently unilateral and association with tension-type headache was present in the women who did not have MO improvement during pregnancy.
Other differences in the clinical variables considered were not statistically significant but nonetheless showed a tendency that is worth studying through a review of broader case series: the women with MO that did not improve during pregnancy had a younger age at onset, an older age at menarche, and a less unfavourable course of their migraine when using oral contraceptives.

Oxidative balance in migraine: an open study by d-ROMs test and BAP test on 50 patients

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Introduction: Migraine is the most common neurological disorder, but the molecular basis is still not completely understood. An impairment of mitochondrial oxidative metabolism might play a role in the pathophysiology. Moreover there is strong evidence associating migraine with a variety of comorbid disorders, including cardiovascular disease and stroke, in which oxidative stress seems to be an important underlying mechanism. However, data are in part controversial and the possible underlying mechanism remain elusive to date and the data regarding the interictal state in migraineurs is limited.
Aim: To evaluate the oxidative balance in a sample of patients with migraine by means of routine specific serum tests, such as d-ROMs test and BAP test.
Methods: 50 outpatients, (32 F, 18 M) mean age 34.8 years (SD 10.9), range 18–58 years, suffering from migraine without aura (ICDH-II 2004 criteria) were enrolled. The mean duration of disease was 1.4 (SD 0.7) years, range 1–3 years. Serum total oxidant capacity was determined by performing the d-ROMs test (2), which 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 H_2O_2), 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 ferric to the ferrous ionic form (optimal value >2,200 μmol/L reduced iron).
Results: Mean values of d-ROMs tests were 385.2 CARR U (SD 119.8) while mean values of BAP test were 1,705.4 μmol/L reduced iron (SD 438.9).
Discussion and conclusions: According to herein reported data, enrolled patients were found to be in a classical condition of oxidative stress. In fact compared to the normal range, oxidant capacity, as measured by means of d-ROMs test, was increased (>300 CARR U) and biological antioxidant potential (as measured by means of BAP test) was decreased (<2,200 μmol/L reduced iron). Although preliminary our study confirm that migraine without aura is associated to oxidative stress and suggests that d-ROMs test and BAP test can be useful to identify an oxidative unbalance in 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 the cause and complications of migraine and may be essential for development of treatment approaches.

Migraine and food intolerance

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Background: Several factors can trigger migraine; among them, dietary factors play a very important role in the onset of migraine attacks. The aim of our study was to evaluate the incidence of food intolerances in a group of migraineurs, by using the Cytotoxic test.
Materials and methods: 80 consecutive patients suffering from migraine and coming to the Headache Centre of S. Luca Hospital, Vallo della Lucania (SA) were examined. 58 were females (F), whose mean age was 33.8 years, range 18–46 years, 22 were males (M), whose mean age was 42.5 years, range 24–56 years. The Cytotoxic test is capable of identifying the presence of specific food intolerances by observing the appearance, the size, the shape or the integrity of leukocytes exposed to extracted food antigens or other materials derived from specific foods.
Results: We found that: 31 F (53.4 %) and 10 M (45.4 %) were intolerant to tyramine. 9 F (15.5 %) and 3 M (13.6 %) were intolerant to milk, 11 F (18.9 %) and 3 M (13.6 %) were intolerant to yeast. 9 F (15.5 %) and 2 M (9.9 %) were intolerant to Solanaceae. 12 F (20.6 %) and no M were (0 %) intolerant to coffee. 13 F (22.4 %) and 1 M (4.5 %) were intolerant to cocoa. 4 F (6.89 %) and no M (0 %) were intolerant to tea. 3 F (5.2 %) and 2 M (9.9 %) were intolerant eggs. 2 F (3.4 %) and 1 M (4.5 %) were intolerant to pork. 3 F (5.2 %) and 1 M (4.5 %) were intolerant to sugar.
Conclusions: Our study showed a high incidence of food intolerance in migraineurs (in females more than in males). The dietary factors which gave more significant results were tyramine, yeast, solanaceae, coffee and cocoa. These results are in agree with those of other studies found in literature, proposing tyramine, coffee and cocoa as very important migraine-precipitating factors. Few are, on the contrary, the evidences of a comorbidity between migraine and intolerance to solanaceae. For this reason, further studies are requested to confirm this hypothesis.

Prophylaxis theraphy of pediatric migraine: an open study with L-tryptophan, Griffonia simplicifolia, vitamin PP and vitamin B6

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Aim: To evaluate the efficacy and tolerability of L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 in prophylaxis therapy of pediatric migraine.
Methods and materials: 18 outpatients, (11 F, 7 M) mean age 10.1 years (SD 4.1), range 4–18 years, suffering from migraine without aura (ICDH'04 criteria) were enrolled. The mean duration of disease was 2.3 (SD 1.2) years, range 1–4 years. At baseline the mean frequency of attacks was 7.2/month (SD 2.2), range 4–12; the mean number of drugs intaking for acute attacks was 6.3 tablets/month (SD 1.4). During the 6 month evaluation period L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 was administered (at dose 100, 480, 18 and 1 mg/die respectively). All patients filled a headache-diary card during the evaluation.
Results: The basal frequency of attack was 7.2 (SD 2.2) and 4.2 (SD 1.9), 3,4 (SD 1.8), 2,5 (SD 2.2), after 1, 3 and 6 months respectively [$P < 0.0001$; $P < 0.0001$; $P < 0.0001$]. The basal value of intaking drugs for acute attacks was 6.3 (SD 1.4) and 3.8 (SD 1.6), 2.9 (SD 1.6), 1.9 (SD1.8) after 1, 3 and 6 months respectively [$P = 0.002$; $P < 0.0001$; $P < 0.0001$] (T test analysis). L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 was well tolerated (7 patients complained somnolence, diarrhoea and gastralgia but none patient withdrew the study).
Conclusions: These data showed a good efficacy in reduction of frequency and intensity of headache attack, a good tolerability and a very good reduction of drugs intaking for acute attacks. Our study suggests that L-tryptophan, griffonia simplicifolia, vitamin PP and vitamin B6 could be an alternative therapy for pediatric migraine prophylaxis.

Migraine and Shiatzu: a preliminary results

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Purpose: Several studies showed that complementary and alternative medicine (CAM) therapies, like Shiatsu, are widely used among primary headache patients, despite few scientific evidence of their benefits. Our aim was to evaluate the effectiveness of Shiatsu versus Amitriptyline in the prophylactic treatment of migraine.
Methods: Patients diagnosed as affected by migraine, and who failed at least one prophylactic drug other than Amytriptiline, were randomly assigned to Shiatsu treatment (group A) or to orally Amitriptyline (group B). Patients in group A underwent weekly sessions for 3 consecutive months in an outpatient neurological setting; orally 10 mg of Amitriptyline daily for 3 consecutive months was administered to patients in group B. The number of days with headache and pain killers per month, as well as the Visual Analogic Scale (VAS) for pain severity, were recorded by means of patient diaries during the 1 month scheduled interviews in the 3 months before the study enrolment and up to 3 month follow-up period. The occurrence of side effects or adverse events were also recorded.
Results: A total of 20 female patients with a mean (±SD) age of 40 ± 15 years, affected by migraine without aura, were enrolled. Each group accounted for 10 patients with similar clinical features. Two patients in the group B reported a mild drowsiness as side effect. After the 3 month follow-up period there was a significant reduction in the mean number of days with headache per month in both group A ($p = 0.05$) and B ($p = 0.04$). The mean number of pain killers per month also decreased in both group A ($p = 0.04$) and B ($p = 0.05$). The VAS score improvement is maintained in group B ($p = 0.04$), but not in A ($p = 0.12$).
Conclusion: Our extended study results suggest that Shiatsu might represent a safe, well tolerated and effective alternative prophylaxis treatment for migraine.
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Survey about headaches in patients with obstructive sleep night apneas

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Introduction: We subjected to study 254 subjects, 173 men and 81 women, average age, suffering from 56.8 + 15.0 syndrome of obstructive sleep night apneas to evaluate the prevalence of headache and put in place a series of preventive measures also in view of preventing complications.
Materials and methods: The subjects were recruited within the Department of Pneumology Teramo Hospital. Apneas are graded as mild (AHI between 5 and 10), moderate (AHI between 11 and 20), severe (AHI > 20). Headaches were classified according to the criteria of HIS. 20 persons (8.1 %) referred to a history of primary headache: 3 affected by Migraine (1.2 %) and 17 (6.9 %) headache. 180 (70.9 %) had headache on awakening, with a greater frequency of breathing pauses during sleep, insomnia central type and episodes of sweating. All were subjected to an interview with a standardised questionnaire on sleep features on related conditions on the type of headache and on risk factors for headache.
Results: At the end of the study, after 2 years, we can say that the severity of obstructive night underlies the morning headache frequency (frequency greater than patients with insomnia), assuming an important role regarding the hypercapnia consequential vasomotor phenomena.
Conclusions: Ultimately, we can say it is appropriate to subject all morning to headache sufferers screening for sleep disturbance related to diseases of the breath, for a correct diagnostic-therapeutic approach in preventive and key.

Author Index

Maxalt RPD® 10 (rizatriptan, MSD)

Riassunto delle caratteristiche del prodotto

1. DENOMINAZIONE DEL MEDICINALE: MAXALT "RPD 5 mg liofilizzato orale". MAXALT "RPD 10 mg liofilizzato orale". **2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA: MAXALT 5 mg:** Ciascun liofilizzato orale contiene 7,265 mg di rizatriptan benzoato (corrispondente a 5 mg di rizatriptan). Eccipienti: aspartame 1,88 mg nel liofilizzato orale da 5 mg. **MAXALT 10 mg:** Ciascun liofilizzato orale contiene 14,53 mg di rizatriptan benzoato (corrispondente a 10 mg di rizatriptan). Eccipienti: aspartame 3,75 mg nel liofilizzato orale da 10 mg. Per un elenco completo degli eccipienti, vedere paragrafo 6.1. **3. FORMA FARMACEUTICA:** Liofilizzati orali. **MAXALT 5 mg:** I liofilizzati orali da 5 mg sono di colore bianco-biancastro, di forma rotonda, con un triangolo modificato su un lato, gusto menta piperita. **MAXALT 10 mg:** I liofilizzati orali da 10 mg sono di colore bianco-biancastro, di forma rotonda, con un quadrato modificato su un lato, gusto menta piperita. **4. INFORMAZIONI CLINICHE. 4.1 Indicazioni terapeutiche:** Trattamento acuto della fase cefalalgica degli attacchi emicranici con o senza aura negli adulti. **4.2 Posologia e modo di somministrazione:** *Generale:* MAXALT liofilizzati orali non deve essere usato per la profilassi. MAXALT liofilizzati orali può essere assunto senza liquidi. Il liofilizzato orale è confezionato in un blister contenuto all'interno di una bustina di alluminio. I pazienti devono essere istruiti a non rimuovere il blister dalla bustina esterna fino al momento immediatamente precedente l'assunzione della dose. La confezione blister deve essere aperta con mani asciutte e il liofilizzato orale deve essere posto sulla lingua, dove si dissolverà e verrà ingerito con la saliva. MAXALT è disponibile anche come formulazione in compresse. Il liofilizzato orale può essere usato nelle situazioni in cui non sono disponibili liquidi, o per evitare la nausea ed il vomito che possono accompagnare l'ingestione delle compresse con i liquidi. *Adulti dai 18 anni in su:* La dose raccomandata è di 10 mg. *Dosi ulteriori:* le dosi devono essere somministrate a distanza di almeno 2 ore l'una dall'altra; nelle 24 ore non devono essere assunte più di 2 dosi. - *in caso di ricomparsa della cefalea entro 24 ore:* se la cefalea si ripresenta dopo la risoluzione dell'attacco iniziale, può essere assunta una ulteriore dose. Osservare i limiti di dosaggio summenzionati. - *in caso di mancato effetto:* negli studi controllati non è stata esaminata l'efficacia di una seconda dose per il trattamento dello stesso attacco, quando una dose iniziale è inefficace. Quindi, se un paziente non risponde alla prima dose, non deve essere assunta una seconda dose per il medesimo attacco. Gli studi clinici hanno mostrato che se un paziente non risponde al trattamento di un attacco, è ancora verosimile che risponda al trattamento per attacchi successivi. Alcuni pazienti devono ricevere la dose più bassa (5 mg) di MAXALT liofilizzati orali, in particolare i gruppi seguenti di pazienti: • pazienti in trattamento con propranololo. Rizatriptan deve essere somministrato a distanza di almeno 2 ore dalla somministrazione di propranololo. (Vedere paragrafo 4.5. • pazienti con insufficienza renale lieve o moderata. • pazienti con insufficienza epatica da lieve a moderata. Le dosi devono essere separate da intervalli di almeno 2 ore; nell'arco delle 24 ore non possono essere assunte più di 2 dosi. *Pazienti pediatrici: Bambini e Adolescenti (età inferiore a 18 anni):* La sicurezza e l'efficacia di MAXALT in bambini e adolescenti di età inferiore a 18 anni non è stata ancora accertata. I dati disponibili al momento sono descritti nei paragrafi 5.1 e 5.2, ma non può essere fatta alcuna raccomandazione su una posologia. *Pazienti oltre 65 anni di età:* La sicurezza e l'efficacia del rizatriptan in pazienti di età superiore ai 65 anni non sono state valutate in modo sistematico. **4.3 Controindicazioni:** Ipersensibilità al rizatriptan o ad uno qualsiasi degli eccipienti. Somministrazione contemporanea di inibitori delle monoaminossidasi (MAO) o l'uso entro le 2 settimane dalla sospensione della terapia con inibitori delle MAO. (Vedere paragrafo 4.5.) MAXALT liofilizzati orali è controindicato in pazienti con insufficienza epatica o renale di grado severo. MAXALT liofilizzati orali è controindicato in pazienti con anamnesi positiva per accidente cerebrovascolare (ACV) o attacco ischemico transitorio (TIA). Ipertensione moderatamente severa o severa, o ipertensione lieve non trattata. Coronaropatia accertata, inclusa cardiopatia ischemica (angina pectoris, anamnesi di infarto del miocardio, o ischemia silente documentata), segni e sintomi di cardiopatia ischemica, o angina di Prinzmetal. Vasculopatia periferica. Uso contemporaneo di rizatriptan ed ergotamina, ergot derivati (inclusa la metisergide) o altri agonisti dei recettori 5-$HT_{1B/1D}$. (Vedere paragrafo 4.5.) **4.4 Avvertenze speciali e precauzioni d'impiego:** MAXALT liofilizzati orali deve essere somministrato solo a pazienti nei quali sia stata fatta una chiara diagnosi di emicrania. MAXALT liofilizzati orali non deve essere somministrato a pazienti con emicrania emiplegica o basilare. MAXALT liofilizzati orali non deve essere usato per trattare cefalee "atipiche", per esempio quelle che possono essere associate a condizioni mediche potenzialmente serie (come ACV, rottura di aneurisma) nelle quali la vasocostrizione cerebrovascolare può essere pericolosa. Rizatriptan può essere associato a sintomi transitori che comprendono dolore ed oppressione toracica i quali possono essere intensi ed interessare la gola (vedere paragrafo 4.8). Qualora si ritenga che tali sintomi indichino una cardiopatia ischemica, non devono essere assunte ulteriori dosi e deve essere effettuata una appropriata valutazione clinica. Come con altri agonisti dei recettori 5-$HT_{1B/1D}$, il rizatriptan non deve essere somministrato, senza una precedente valutazione, a pazienti nei quali è probabile una malattia cardiaca non diagnosticata o a pazienti a rischio per cardiopatia coronarica (CAD) [ad es., pazienti con ipertensione, diabete mellito, fumatori o coloro che fanno uso di terapia nicotinica sostitutiva, uomini di età superiore ai 40 anni, donne in età postmenopausale, pazienti con blocco di branca e coloro con una importante anamnesi familiare di CAD]. Le valutazioni cardiologiche possono non identificare tutti i pazienti con patologia cardiaca e, in casi molto rari, si sono verificati seri eventi cardiaci in pazienti senza una cardiopatia di base dopo somministrazione di $5HT_1$ agonisti. I pazienti con CAD accertata non devono essere trattati con MAXALT liofilizzati orali. (Vedere paragrafo 4.3.) Gli agonisti dei recettori 5-$HT_{1B/1D}$ sono stati associati con vasospasmo coronarico. In rari casi, con l'uso degli agonisti dei recettori $5HT_{1B/1D}$, compreso MAXALT, sono stati riportati ischemia o infarto del miocardio (vedere paragrafo 4.8). Altri agonisti 5- $HT_{1B/1D}$ (ad es., il sumatriptan) non devono essere usati contemporaneamente con MAXALT liofilizzati orali. (Vedere anche paragrafo 4.5.) E' opportuno attendere almeno 6 ore dall'uso di rizatriptan prima di somministrare farmaci ergotamino-simili (ad es., ergotamina, diidroergotamina o metisergide). Prima che sia somministrato il rizatriptan devono trascorrere almeno 24 ore dalla somministrazione di una preparazione contenente ergotamina. Sebbene in uno studio di farmacologia clinica su 16 soggetti maschi sani trattati con rizatriptan per os e ergotamina per via parenterale non siano stati osservati effetti vasospastici addizionali, questi sono teoricamente possibili. (Vedere paragrafo 4.3.) La sindrome da serotonina (inclusi alterazione dello status psichico, instabilità autonomica e anormalità neuromuscolare) è stata segnalata a seguito di trattamento concomitante con triptani e inibitori selettivi della ricaptazione della serotonina (SSRI) o inibitori della ricaptazione della serotonina-noradrenalina (SNRI). Queste reazioni possono essere gravi. Se il trattamento concomitante con rizatriptan e un SSRI o un SNRI è giustificato dal punto di vista clinico, si consiglia di tenere il paziente sotto appropriata osservazione, in particolare durante la fase iniziale del trattamento, in caso di aumento del dosaggio, o nel caso venga aggiunto alla terapia un altro medicinale serotonergico. (Vedere paragrafo 4.5.) Gli effetti indesiderati possono verificarsi con maggiore frequenza con l'uso concomitante di triptani (5-$HT_{1B/1D}$ –agonisti) e di preparazioni a base di erbe che contengono Erba di S. Giovanni (Hypericum perforatum). In pazienti trattati con triptani, fra i quali rizatriptan, può verificarsi angioedema (per es. edema del volto, gonfiore della lingua ed edema faringeo). In caso di angioedema della lingua o del faringe il paziente deve essere posto sotto osservazione medica fino a risoluzione dei sintomi. Il trattamento deve essere immediatamente interrotto e sostituito con un farmaco di classe diversa. *Fenilchetonurici*: Pazienti con fenilchetonuria devono essere informati che la fenilalanina può essere dannosa. I liofilizzati orali di MAXALT contengono aspartame(che contiene fenilalanina). Ciascun liofilizzato orale da 5 mg contiene 1,88 mg di aspartame e ciascun liofilizzato orale da 10 mg contiene 3,75 mg di aspartame. Quando il rizatriptan è somministrato a pazienti in terapia con substrati del CYP 2D6, deve essere considerata la potenzialità di interazione (Vedere paragrafo 4.5). *Cefalea da uso eccessivo di farmaci:* L'uso prolungato di qualsiasi antidolorifico per la cefalea può peggiorarla. In caso si verifichi o si sospetti questa evenienza, si deve ottenere un parere medico e interrompere il trattamento. La diagnosi di cefalea da uso eccessivo di farmaci deve essere sospettata in pazienti con cefalee frequenti o giornaliere nonostante l'uso regolare di farmaci per la cefalea (o a causa di esso). **4.5 Interazioni con altri medicinali ed altre forme di interazione:** Ergotamina, ergot derivati (inclusa la metisergide), altri agonisti del recettore 5 $HT_{1B/1D}$: a causa di un effetto additivo, l'uso concomitante di rizatriptan e di ergotamina, di ergot derivati (inclusa la metisergide), o di altri agonisti del recettore 5 $HT_{1B/1D}$ (per es.: sumatriptan, zolmitriptan, naratriptan) aumenta il rischio di vasocostrizione delle arterie coronarie e di effetti ipertensivi. Questa associazione è controindicata. (Vedere paragrafo 4.3.) *Inibitori delle monoaminoossidasi:* Il rizatriptan è metabolizzato principalmente tramite la monoaminossidasi tipo A (MAO-A). Le concentrazioni plasmatiche del rizatriptan e del suo metabolita attivo N-monodesmetile venivano incrementate dalla somministrazione contemporanea di un inibitore della MAO-A selettivo e reversibile. Con inibitori delle MAO non selettivi, reversibili (per es.: linezolid) e irreversibili sono previsti effetti simili o maggiori. A causa del rischio di vasocostrizione delle arterie coronarie e di episodi ipertensivi, la somministrazione di MAXALT liofilizzati orali a pazienti che assumono inibitori delle MAO è controindicata. (Vedere paragrafo 4.3.) *Beta-bloccanti:* Le concentrazioni plasmatiche del rizatriptan possono essere aumentate dalla contemporanea somministrazione di propranololo. Questo incremento è per lo più dovuto all'interazione nel metabolismo di primo passaggio tra i due farmaci, poiché la MAO-A gioca un ruolo nel metabolismo sia del rizatriptan che del propranololo. Questa interazione porta ad un incremento medio dell'AUC e della C_{max} del 70-80%. In pazienti in terapia con propranololo, deve essere usata la dose da 5 mg di MAXALT liofilizzati orali. (Vedere paragrafo 4.2.) In uno studio sull'interazione fra farmaci, nadololo e metoprololo non hanno alterato le concentrazioni plasmatiche del rizatriptan. *Inibitori selettivi della ricaptazione della serotonina (SSRI)/Inibitori della ricaptazione della serotonina-noradrenalina (SNRI) e sindrome della serotonina:* vi sono state segnalazioni di pazienti con sintomi compatibili con la sindrome da serotonina (inclusi alterazione dello status psichico, instabilità autonomica e anormalità neuromuscolari) dopo l'uso di inibitori selettivi della ricaptazione della serotonina (SSRI) o inibitori della ricaptazione della serotonina-noradrenalina (SNRI) e triptani (vedere paragrafo 4.4). Studi *in vitro* indicano che il rizatriptan *in vitro* inibisce il citocromo P450 2D6 (CYP 2D6) . Non sono disponibili dati sull'interazione clinica. Quando il rizatriptan è somministrato a pazienti che assumono substrati del CYP 2D6, deve essere considerata la potenziale interazione. **4.6 Gravidanza e allattamento:** *Uso in gravidanza:* La sicurezza dell'uso del rizatriptan durante la gravidanza nella specie umana non è stata accertata. Gli studi su animali a livelli di dosaggio superiori a quelli terapeutici non indicano effetti dannosi sullo sviluppo dell'embrione o del feto, né sul corso della gestazione, del parto e dello sviluppo postnatale. Poiché studi di riproduzione e sviluppo nell'animale non sono sempre predittivi della risposta nell'uomo, MAXALT liofilizzati orali deve essere usato durante la gravidanza solo in caso di effettiva necessità. *Uso durante l'allattamento:* Studi nei ratti hanno indicato che si è verificato un passaggio molto elevato di rizatriptan nel latte. Riduzioni transitorie e molto scarse dei pesi corporei dei cuccioli prima dello svezzamento, sono state osservate solo quando l'esposizione sistemica materna eccedeva molto rispetto ai livelli di esposizione massima per l'uomo. Non esistono dati nell'uomo. Quindi, deve essere esercitata cautela quando si somministra il rizatriptan a donne che allattano. L'esposizione dei neonati deve essere minimizzata evitando l'allattamento per le 24 ore successive al trattamento. **4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari:** L'emicrania o il trattamento con MAXALT liofilizzati orali possono causare sonnolenza in alcuni pazienti. In alcuni pazienti in terapia con MAXALT liofilizzati orali è stato anche riportato capogiro. I pazienti perciò devono valutare la loro capacità di svolgere attività complesse durante gli attacchi emicranici e dopo la somministrazione di MAXALT liofilizzati orali. **4.8 Effetti indesiderati:** MAXALT (sia in compressa che in liofilizzato orale) è stato valutato in oltre 3.600 pazienti adulti fino ad un anno in studi clinici controllati. Gli effetti indesiderati più comuni valutati negli studi clinici sono stati capogiro, sonnolenza e astenia/affaticamento. I seguenti effetti indesiderati sono stati valutati negli studi clinici e/o riportati nell'esperienza post-marketing: *[Molto comune (≥ 1/10); Comune (≥1/100,*

<1/10); Non comune (≥1/1.000, < 1/100) Raro (≥ 1/10.000, < 1/1.000), Molto raro (≤ 1/10.000), non nota (la frequenza non puo essere definita sulla base dei dati disponibili)]. ***Disturbi del sistema immunitario:*** *Non comune:* reazione di ipersensibilità. *Raro*: anafilassi/reazione anafilattoide. ***Disturbi psichiatrici:*** *Non comune*: disorientamento, insonnia, nervosismo. ***Patologie del sistema nervoso:*** *Comune*: capogiro, sonnolenza, parestesie, cefalea, ipoestesia, diminuzione dell'acutezza mentale, tremore. *Non comune*: atassia, vertigini. *Raro*: disgeusia/alterazione del gusto, sincope, sindrome da serotonina. *Non nota*: convulsioni. ***Patologie dell'occhio:*** *Non comune*: visione offuscata. ***Patologie cardiache:*** *Comune*: palpitazioni, tachicardia. *Raro*: ischemia o infarto del miocardio, accidente cerebrovascolare. La maggior parte di queste reazioni avverse sono state segnalate in pazienti con fattori di rischio predittivi di coronaropatia. *Non nota*: aritmia, bradicardia. ***Patologie vascolari:*** *Comune*: vampate. *Non comune*: ipertensione. *Non nota*: ischemia vascolare periferica. ***Patologie respiratorie, toraciche e mediastiniche:*** *Comune*: disturbi faringei, dispnea. *Raro*: sibilo respiratorio. ***Patologie gastrointestinali:*** *Comune*: nausea, secchezza delle fauci, vomito, diarrea. *Non comune*: sete, dispepsia. *Non nota*: colite ischemica. ***Patologie della cute e del tessuto sottocutaneo:*** *Comune*: arrossamento, sudorazione, eruzione cutanea. *Non comune*: prurito, orticaria, angioedema (per es.: edema del volto, gonfiore della lingua, edema della faringe) (per l'angioedema, vedere anche paragrafo 4.4). *Raro*: necrolisi epidermica tossica. ***Patologie del sistema muscoloscheletrico e del tessuto connettivo:*** *Comune*: pesantezza locale. *Non comune*: dolore cervicale, irrigidimento locale, rigidità, debolezza muscolare. *Raro*: dolore al viso. *Non nota*: mialgia. ***Patologie sistemiche e condizioni relative alla sede di somministrazione:*** *Comune*: astenia/affaticamento, dolore addominale o toracico. ***Esami diagnostici:*** *Non nota*: anomalie dell'ECG. **4.9 Sovradosaggio:** Rizatriptan 40 mg (somministrato o in compresse in singola dose o in due dosi con un intervallo di 2 ore) è stato generalmente ben tollerato in più di 300 pazienti adulti; capogiro e sonnolenza sono stati gli effetti indesiderati correlati al farmaco più comuni. In uno studio di farmacologia clinica, dove 12 soggetti adulti hanno ricevuto rizatriptan a dosi cumulative totali di 80 mg (somministrate nell'arco di 4 ore), due soggetti hanno riportato sincope e/o bradicardia. Un soggetto, una donna di 29 anni, ha sviluppato vomito, bradicardia e capogiro 3 ore dopo aver ricevuto un totale di 80 mg di rizatriptan (somministrato nell'arco di 2 ore). Un blocco AV di terzo grado, responsivo alla atropina, è stato osservato un'ora dopo l'inizio degli altri sintomi. Il secondo soggetto, un uomo di 25 anni, ha accusato transitori capogiri, sincope, incontinenza, e una pausa sistolica della durata di 5 secondi (registrata mediante ECG) immediatamente dopo una venopuntura dolorosa. La venopuntura era stata effettuata 2 ore dopo che il soggetto aveva ricevuto un totale di 80 mg di rizatriptan (somministrato nell'arco di 4 ore). Inoltre, sulla base della farmacologia del rizatriptan, dopo un sovradosaggio potrebbero verificarsi ipertensione od altri sintomi cardiovascolari più seri. Nel caso si sospetti un sovradosaggio di MAXALT liofilizzati orali, si deve prendere in considerazione la disintossicazione gastrointestinale (ad es., lavanda gastrica seguita da carbone attivo). Il monitoraggio clinico ed elettrocardiografico deve durare almeno 12 ore, anche in assenza di sintomi clinici. Gli effetti dell'emodialisi o della dialisi peritoneale sulle concentrazioni sieriche di rizatriptan sono sconosciuti. **5. PROPRIETA' FARMACOLOGICHE. 5.1 Proprietà farmacodinamiche:** *Meccanismo d'azione:* agonisti selettivi ($5HT_{1B/1D}$) della serotonina. Categoria farmacoterapeutica: Codice ATC: N02C C04. Rizatriptan si lega selettivamente con elevata affinità ai recettori $5\text{-}HT_{1B}$ e $5\text{-}HT_{1D}$ umani ed ha scarso o nullo effetto o attività farmacologica a livello dei recettori $5\text{-}HT_2$, $5\text{-}HT_3$, a livello dei recettori α_1, α_2- o b-adrenergici, D_1, D_2, dopaminergici, H_1 istaminici, muscarinici o delle benzodiazepine. L'attività terapeutica del rizatriptan nel trattamento della cefalalgia emicranica può essere attribuita al suo effetto agonista a livello dei recettori $5\text{-}HT_{1B}$ e $5\text{-}HT_{1D}$ dei vasi sanguigni intracranici extracerebrali che si pensa si dilatino durante un attacco e sui nervi sensoriali del trigemino che li innervano. L'attivazione di questi recettori $5\text{-}HT_{1B}$ e $5\text{-}HT_{1D}$ può comportare la costrizione dei vasi sanguigni intracranici che generano il dolore e l'inibizione del rilascio neuropeptidico che comporta una ridotta infiammazione dei tessuti sensitivi ed una ridotta trasmissione centrale del segnale doloroso trigeminale. *Effetti farmacodinamici: Adulti:* L'efficacia di MAXALT liofilizzati orali nel trattamento acuto degli attacchi di emicrania è stata dimostrata in due studi multicentrici, randomizzati, controllati con placebo, che avevano un disegno simile agli studi su MAXALT compresse. In uno studio (n=311), a due ore dalla somministrazione, le percentuali di sollievo dai sintomi in pazienti trattati con MAXALT liofilizzati orali sono state approssimativamente del 66% per rizatriptan 5 mg e 10 mg, rispetto al 47% del placebo. In uno studio più ampio (n=547), a due ore dalla somministrazione, le percentuali di sollievo dai sintomi sono state del 59% nei pazienti trattati con MAXALT liofilizzati orali da 5 mg e del 74% con il 10 mg, rispetto al 28% del gruppo placebo MAXALT liofilizzati orali ha anche attenuato la disabilità, la nausea, la fotofobia e la fonofobia che accompagnano gli episodi emicranici. In uno dei due studi clinici effettuati per la dose di 10 mg è stato osservato un effetto significativo sul sollievo dal dolore già 30 minuti dopo l'assunzione della dose (vedere paragrafo 5.2). Sulla base di studi effettuati per la formulazione in compresse orali, rizatriptan conferma la sua efficacia nel trattamento dell'emicrania mestruale, cioè dell'emicrania che si manifesta entro i tre giorni prima o dopo l'inizio del ciclo mestruale. *Adolescenti (12-17 anni di età):* L'efficacia di MAXALT liofilizzati orali in pazienti pediatrici (da 12-17 anni di età) è stata valutata in uno studio multicentrico, randomizzato, in doppio cieco, controllato con placebo, a gruppi paralleli (n=570). Si richiedeva che la popolazione di pazienti fosse anamnesticamente non responsiva alla terapia con FANS e paracetamolo. I pazienti con una cefalea di tipo emicranico qualificante inizialmente sono stati trattati con placebo o rizatriptan nei 30 minuti successivi all'insorgenza. Dopo 15 minuti di run-in con il placebo, i soggetti che non avevano risposto al placebo hanno poi trattato un singolo attacco di emicrania con placebo o rizatriptan. Usando una strategia di dosaggio basata sul peso, i pazienti di peso da 20 kg a <40 kg hanno ricevuto 5 mg di rizatriptan e i pazienti di peso ≥40 kg hanno ricevuto 10 mg di rizatriptan. In questa popolazione di studio arricchita, è stata osservata una differenza del 9% tra il trattamento attivo ed il placebo per l'endpoint primario di efficacia di libertà dal dolore (riduzione da dolore moderato o grave a nessun dolore) 2 ore dopo il trattamento (31 % con rizatriptan verso il 22 % con placebo (p=0,025)). Non è stata trovata alcuna differenza significativa per l'endpoint secondario di sollievo dal dolore (riduzione da dolore moderato o grave a lieve o nessun dolore). *Bambini (6-11 anni di età):* L'efficacia di MAXALT liofilizzati orali è stata valutata anche in pazienti pediatrici da 6 a 11 anni di età nello stesso studio clinico in acuto controllato con placebo (n=200). La percentuale di pazienti che raggiungevano la libertà dal dolore 2 ore dopo il trattamento non è stata significativamente differente da un punto di vista statistico nei pazienti che avevano ricevuto MAXALT liofilizzati orali da 5 e 10 mg, rispetto a quelli che avevano ricevuto placebo (39,8% verso 30,4% p=0,269). MAXALT liofilizzati orali permette ai pazienti con emicrania di trattare il loro attacchi emicranici senza bisogno di ingerire liquidi. Questo può permettere ai pazienti di assumere prima il loro farmaco, per esempio, quando i liquidi non sono disponibili e di evitare il possibile peggioramento dei sintomi gastrointestinali dovuti alla ingestione di liquidi. **5.2 Proprietà farmacocinetiche:** *Assorbimento:* Rizatriptan viene rapidamente e completamente assorbito dopo somministrazione orale. La biodisponibilità orale media del liofilizzato orale è approssimativamente del 40-45%, e i valori medi delle concentrazioni plasmatiche massime (C_{max}) sono raggiunti in circa 1,58 ore (T_{max}). Il tempo per il raggiungimento della concentrazione plasmatica massima dopo somministrazione di rizatriptan come formulazione liofilizzati orali è ritardata di 30-60 minuti rispetto alla compressa. *Effetti degli alimenti*: gli effetti degli alimenti sull'assorbimento di rizatriptan liofilizzato orale non sono stati studiati. Per il rizatriptan compresse, la T_{max} viene ritardata di circa 1 ora dalla somministrazione a stomaco pieno. Un ritardo ulteriore dell'assorbimento di rizatriptan può verificarsi quando viene somministrato dopo i pasti il liofilizzato orale. *Distribuzione:* Rizatriptan è legato in minima parte (14%) alle proteine plasmatiche. Il volume di distribuzione è approssimativamente di 140 litri in soggetti di sesso maschile e di 110 litri in soggetti di sesso femminile. *Biotrasformazione:* La via primaria del metabolismo del rizatriptan è la deaminazione ossidativa da parte della monoaminossidasi-A (MAO-A) nel metabolita acido indolacetico, che è farmacologicamente inattivo. In misura minore si forma l'N-monodesmetil-rizatriptan, un metabolita con attività simile a quella del composto progenitore a livello dei recettori $5\text{-}HT_{1B/1D}$, ma che non contribuisce significativamente all'attività farmacodinamica del rizatriptan. Le concentrazioni plasmatiche del N-monodesmetil-rizatriptan sono approssimativamente il 14% di quelle del composto progenitore ed è eliminato in simile quantità. Altri metaboliti minori comprendono l'N-ossido, il composto 6-idrossilato, e la forma coniugata con il solfato del metabolita 6-idrossilato. Nessuno di questi metaboliti minori è farmacologicamente attivo. Dopo somministrazione orale di rizatriptan marcato con ^{14}C, rizatriptan è responsabile di circa il 17% della radioattività plasmatica circolante. *Eliminazione:* Dopo somministrazione endovenosa, l'AUC aumenta, proporzionalmente nell'uomo e quasi proporzionalmente nella donna, con la dose nel *range* di dosaggio 10-60 mg/kg. In seguito a somministrazione orale, l'AUC aumenta in modo quasi proporzionale con la dose in un *range* di dosaggio di 2,5-10 mg. L'emivita plasmatica del rizatriptan in uomini e donne è in media 2-3 ore. La *clearance* plasmatica del rizatriptan è in media circa 1000-1500 ml/min negli uomini e circa 900-1100 ml/min nelle donne; circa il 20-30% di questa è dato dalla *clearance* renale. Dopo una dose orale di rizatriptan marcato con ^{14}C, circa l'80% della radioattività è escreta con le urine e circa il 10% della dose è escreta con le feci. Ciò dimostra che i metaboliti sono escreti principalmente per via renale. In accordo con il suo metabolismo di primo passaggio, approssimativamente il 14% di una dose orale è escreto con le urine come rizatriptan immodificato mentre il 51% è escreto come metabolita acido indolacetico. Non più dell'1% è escreto con le urine come il metabolita N-monodesmetilato attivo. Se il rizatriptan è somministrato secondo il regime di dosaggio massimo, non si verifica accumulo plasmatico del farmaco giorno dopo giorno. *Caratteristiche dei pazienti:* I dati seguenti sono basati su studi con la formulazione di compresse orali. *Pazienti con un attacco emicranico:* Un attacco emicranico non interferisce con la farmacocinetica del rizatriptan. *Sesso*: Negli uomini rispetto alle donne, l'AUC del rizatriptan (10 mg somministrati per os) è risultata di circa il 25% più bassa, la C_{max} dell'11% più bassa e il T_{max} è stato raggiunto approssimativamente nello stesso momento. Questa apparente differenza farmacocinetica non è stata di rilevanza clinica. *Anziani*: Le concentrazioni plasmatiche del rizatriptan osservate in soggetti anziani (età compresa tra 65 e 77 anni) dopo la somministrazione di compresse sono state simili a quelle osservate in adulti giovani. *Pazienti pediatrici:* Uno studio di farmacocinetica del rizatriptan (formulazione in liofilizzati orali) è stato condotto in pazienti pediatrici emicranici da 6 a 17 anni di età. Le esposizioni medie dopo somministrazione di una dose singola di 5 mg di rizatriptan liofilizzati orali a pazienti pediatrici di peso compreso tra 20-39 kg o di 10 mg di rizatriptan liofilizzati orali a pazienti pediatrici di peso ≥40 Kg sono state rispettivamente del 15% inferiore e del 17 % superiore rispetto alla esposizione osservata dopo somministrazione di una dose singola di 10 mg di rizatriptan liofilizzati orali a pazienti adulti. La rilevanza clinica di queste differenze non è chiara. *Compromissione epatica (punteggio di Child-Pugh 5-6):* Dopo somministrazione orale di compresse in pazienti con danno epatico causato da lieve cirrosi epatica alcolica, le concentrazioni plasmatiche del rizatriptan sono risultate simili a quelle osservate in soggetti giovani di ambo i sessi. Un incremento significativo dell'AUC (50%) e della C_{max} (25%) è stato osservato in pazienti con danno epatico moderato (punteggio di Child-Pugh 7). La farmacocinetica non è stata studiata in pazienti con punteggio di Child-Pugh >7 (danno epatico severo). *Compromissione renale:* In pazienti con compromissione della funzione renale (clearance della creatinina 10-60 ml/min/1,73m^2), l'AUC del rizatriptan dopo la somministrazione di compresse non è stata significativamente differente da quella osservata nei soggetti sani. In pazienti in emodialisi (*clearance* della creatinina <10 ml/min/1,73m^2) l'AUC del rizatriptan è stata approssimativamente maggiore del 44% rispetto a quella osservata in pazienti con funzione renale normale. La concentrazione plasmatica massima del rizatriptan in pazienti con compromissione renale di qualsiasi grado è stata simile a quella di soggetti sani. **5.3 Dati preclinici di sicurezza:** I dati preclinici indicano l'assenza di rischio per l'uomo sulla base di studi convenzionali di tossicità per dosi ripetute, genotossicità, cancerogenicità potenziale, tossicità sulla riproduzione e sullo sviluppo, sicurezza farmacologica, nonché di farmacocinetica e metabolismo. **6. INFORMAZIONI FARMACEUTICHE. 6.1 Elenco degli eccipienti:** Gelatina, mannitolo (E421), glicina, aspartame (E951), aroma di menta piperita (composto di olio di menta piperita, maltodestrina e destrina). **6.2 Incompatibilità:** Non applicabile. **6.3 Periodo di validità:** 3 anni. **6.4 Precauzioni particolari per la conservazione:** Non conservare a temperatura superiore ai 30° C. **6.5 Natura e contenuto del contenitore:** Blister in alluminio/PVC/PVDC con 1 liofilizzato orale contenuto in una bustina di alluminio. Confezioni da 2, 3, 6, 12 o 18 liofilizzati orali. E' possibile che non tutte le confezioni siano commercializzate. **6.6 Precauzioni particolari per lo smaltimento:** Il medicinale non utilizzato ed i rifiuti derivati da tale medicinale devono essere smaltiti in conformità alla normativa locale vigente. **7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO:** MSD Italia S.r.l. Via Vitorchiano, 151 – 00189 Roma. **8. NUMERO DI A.I.C.:** "RPD" 3 liofilizzati orali 5 mg n. 034115079/M. "RPD" 6 liofilizzati orali 5 mg n. 034115081/M. "RPD" 12 liofilizzati orali 5 mg n. 034115093/M. "RPD" 3 liofilizzati orali 10 mg n. 034115105/M. "RPD" 6 liofilizzati orali 10 mg n. 034115117/M. "RPD" 12 liofilizzati orali 10 mg n. 034115129/M. **9. DATA DELLA PRIMA AUTORIZZAZIONE / DEL RINNOVO DELL'AUTORIZZAZIONE:** Data della prima autorizzazione: Maggio 1999. Data dell'ultimo rinnovo: Aprile 2008. **10. DATA DI REVISIONE DEL TESTO:** Febbraio 2012.

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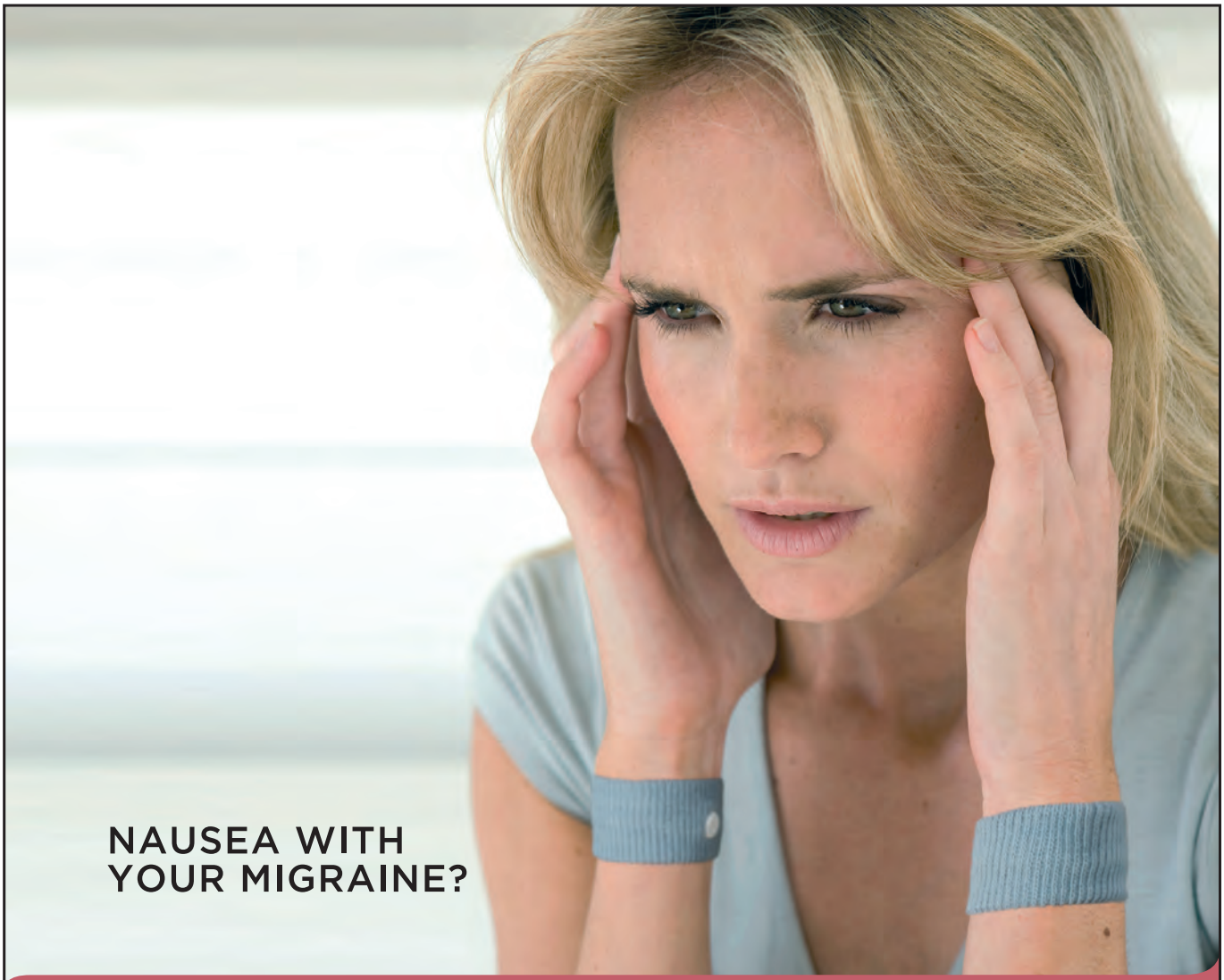

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