



# **XIX National Congress of the Italian Society for the Study of Headaches**

**Patient and headache: from care to cure**  
**The future of therapy from the itineraries of the past**

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**Proceedings**

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It is a great satisfaction and privilege for me to introduce the proceedings of the XIX National Congress of the Italian Society for the Study of Headaches “*Patient and headache: from care to cure – The future of therapy from the itineraries of the past*”.

A very significant title indeed, which underlies the importance of the centrality of the patient-physician relationship, as always considering the entire history of medicine; and at the same time, from a perspective of continuity with the past, highlights how today in the headache field we can offer, along with caring, better therapeutic strategies aimed at curing thanks to innovative drugs of increasing selectivity and efficacy.

The topics of the Congress are of great relevance and range from recent developments in genetics to new neurophysiological acquisitions, from headaches in childhood and adolescence to the psychobiological aspects of headaches, from critical evaluation of the ICHD-II to comorbidity, and from TACs and cranial neuralgias to headache management in the Emergency Department. Special attention has been given to the always present problem of chronic headaches, and to the present and future advancements in therapy. Three important round tables will be dedicated to patient associations, problems in the continuity of health care, and the first evaluation of the regionalization of the Society, which has at this point been completed. Lastly, a significant number of oral communications of high scientific interest attests to the vivacity and the active participation of numerous members of the Society. I would like to thank those who have contributed to this issue of the Journal, in particular, the Scientific Secretariat who evaluated all the abstracts and the referees who reviewed the short papers.

From these proceedings two aspects which characterise the Italian Society for the Study of Headaches stand out: the Society’s highly professional and scientific profile and its multidisciplinary nature. This is emphasised by the presence of different and complementary headache specialists, who by working together are able to provide integrated answers to basic and clinical problems, to ultimately meet patients’ needs and to relieve their suffering.

The location of the Congress in Padua and in Venice is both artistically exciting and historically meaningful: the University of Padua, recognized as “the cradle of modern medicine”; and Venice, the “Dominant”, the capital of Saint Mark’s Republic, the government of which knew how to promote with great foresight and generosity the advancement of knowledge of its “Studium Generale”. An implicit reminder of the constant need, today,

as in the past for continuous cooperation not only between scientists and governments but also between clinical medicine and health planning.

I warmly welcome all the participants both to Padua, an historical centre of excellence for the progress of scientific research, and to Venice, the core of art and beauty, “the city of the spirit and dreams”. I wish all of you a very productive and enjoyable Congress.

*Giorgio Zanchin*  
*President*  
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Giorgio Zanchin\*

## Padua, the cradle of modern medicine: Bernardino Ramazzini (1633–1714) on headaches

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**Abstract** A prominent historian of Medicine, Henry Sigerist, quoted the Padua Medical School as “the cradle of modern medicine”. This opinion is currently accepted worldwide. A short outline on the contribution of the Padua Medical School to the development of medical knowledge in its “golden age” is given. In this context, the work of a prominent figure of the 17th century Padua University and the founder of Occupational Medicine, Bernardino Ramazzini, is considered, with focus on his interest in headache.

**Key words** Ramazzini • Headache • History of medicine • Padua University Medical School

Medical historians agree on the extraordinary role played by the Paduan School in the development of medical knowledge between the 15th and 16th centuries. A second flourishing season took place in the 18th century, with the foundation of Occupational Medicine by Ramazzini [1], and with the shift from humoral galenic medicine to solidistic medicine, through the anatomico-clinical method by Morgagni.

We will try to briefly examine the 16th century golden age first, focusing secondly on the contribution of Ramazzini, specifically to headache.

The fourth decade of the 16th century in Padua represents a turning point in the modern history of medicine.

Here, in the same year, 1543, when Andreas Vesalius' (1514–1564) *De humani corporis fabrica* was published, Giovanni Battista da Monte (1489–1551) originated the method of clinical instruction at the bedside of the patient at the San Francesco Grande Hospital. Therefore, the critical attitude of the Renaissance anatomist had, in a sense, its immediate clinical counterpart with the physician teaching at the bedside of the sick.

Moreover, in 1545, the realisation of the Botanical Gardens permitted the “ostensio simplicium”, that is, the demonstration of real plants, developed from the “lectura simplicium”, or, the single literary description of the sub-

ject. A year later, Girolamo Fracastoro, in his *De contagione et contagiosis morbis*, was the first to hypothesise the presence of “seminaria morbi”, foreseeing the microbial theories established only three centuries later.

Therefore, it can be said that in those years Padua was the centre of the medical Renaissance as Florence was the centre of the artistic Renaissance.

The precedents to these outstanding developments go back almost to the origin of the Padua University (1222). In those years, the rediscovery of numerous classical, philosophical and medical writings took place. In particular, the knowledge of the so-called “physical” writings of Aristotle stimulated renewed attention in the study of nature in opposition to theological themes. As an expression of these interests, at the end of the 1300s, the dissection of the human body began to be performed in the Bologna-Padua area. However, at first the influence of Galen, whose teachings were transmitted in an acritical manner, strictly prevailed, and were emblematically represented by the modality with which the lessons of anatomy were carried out: the professor merely commented *ex cathedra* upon the galenic text, without assuming any direct role in the dissection.

With the Venetian expansion of 1405, Padua became the site of the state university of Saint Mark’s Republic. As we have seen, in our town the studies had assumed a philosophical direction that privileged the empiristic contents of the biological works of Aristotle and favoured, as a result, the observation of nature, an essential aspect of the revival of the anatomical investigations. In this regard, it is useful to remember that from the mid 1400s, examination of the cadaver for academic interest was already codified in the statute of the Paduan School, which established the obligation to proceed yearly with the anatomical dissection of at least two human bodies.

It was upon this background that the activity of the pre-Vesalian anatomists in Padua was situated, and in particular, the teaching of Alessandro Benedetti (1455–ca. 1525), who realised the construction of an anatomical theatre which could be disassembled, aimed at improving instruction based precisely upon objectivity. After Vesalius (1514–1564) followed Realdus Columbus (1516–1559), who first described the lesser circulation, and later Gabrielis Falloppius (1523–1562), who greatly contributed to the knowledge of the cranial nerves and of the female reproductive system.

We have thus arrived at the great moment of the Paduan School of Medicine. It is the golden era of the “Patavina Universitas”, attended by foreign students who converged from all of the European countries.

Indeed, the permanent theatre that Fabrici d’Acquapendente (1533–1619), the successor to Falloppius, had erected in 1594, became the model of the demonstrative teaching of anatomy in the various

European Universities, such that similar structures were to be built by pupils returning from medical studies in Padua to universities such as Leiden, Copenhagen, Basel and Uppsala. Among the other great accomplishments of d’Acquapendente, we limit ourselves to remember his embryological studies, the description of the venous valves, and the realisation of a collection of coloured anatomical paintings, which he bequeathed in his testament to the Venetian State. For this anatomical atlas, d’Acquapendente is credited with being the first to sense the importance of coloured illustrations for anatomical preparations. D’Acquapendente was also the teacher of William Harvey (1578–1657), the discoverer of the circulation of the blood. Attracted to Padua by the reputation of its University, the young Englishman arrived in the city to further his studies, receiving a doctorate’s degree in medicine in 1602. The outstanding discovery of William Harvey is recognised as directly connected with his Paduan education, because here he learned of the existence of the valves of the veins, a unidirectional structure, from d’Acquapendente, and of the connections between mathematics and research within the experimental method from Galilei.

Let us now focus on a prominent character of the second flourishing season of the Paduan Medical School, which took place at the beginning of the 18th century.

Bernardino Ramazzini was born in 1633 in Carpi, near Modena. He graduated from Parma in Philosophy and Medicine in 1659. A year later, he obtained an appointment as district medical officer in the Viterbo countryside. Malarial fever forced him to return to his native city. Later, he moved to Modena, where, in 1682, he was nominated head professor of Medical Institutions and Theoretical Medicine at the “Studio Pubblico di S. Carlo”, the renowned University of Modena, and became court physician of the Duke of Este. In 1700, after almost 30 years in Modena, he was called by the Venetian Senate to the University of Padua. Here, he died of a cerebral haemorrhage, after 14 years of untiring clinical activity and teaching. Our investigations, recently published in *The Lancet* [2], confirmed the traditional belief that the mortal remains of the great physician rest “sine titulo” in the present-day oratory of San Francesco di Sales in Padua. Another recent study allowed us to identify the house where Ramazzini lived.

His scientific production is rich and varied [3]. Most important among his works is *De morbis artificum diatriba*, which lays down the foundation of modern Occupational Medicine. The volume appeared in two editions [4, 5]: in 1700 (Modena), and in 1713 (Padua), enlarged by a supplement. Some personal experiences, among which the observation on a daily basis, during the appointment as district medical officer, of the extremely

poor working conditions of local dwellers, and of some sewer maintenance workers at his own residence in Modena, contributed to drawing the attention of Ramazzini to the diseases of the working class [6].

Among the 69 professions described, accounting for the majority of the occupations of the period, headache is quoted in 15 instances, 12 of which as a disturbance directly related to working conditions. The main categories involved are, according to Ramazzini: pharmacists, carpenters, brewers, tobacco workers and oil producers, confectioners, desk workers and stenographers, Jewish women, lackeys and runners, hunters and sailors, wet-nurses, those working with wine and beer, sewer cleaners, musicians and singers, and soldiers [7]. His remarks on headache are typical of his way of collecting first-hand experience of working conditions, and they underline the importance of occupational hazards in the assessment of headache. In keeping with his clinical approach, he visited the workplaces in person, observing the sanitary conditions, and interrogated the patient in detail on his activities. Ramazzini was really interested in headache and its different aspects, especially as he had often had first-hand experience. From what he writes about his own reaction to bad smells in grimy shops, we may infer that he himself was suffering from migraine.

The importance of a particular contribution given by Ramazzini was recently shown, after nearly two centuries, by the research conducted by our Headache Centre regarding osmophobia. Bernardino Ramazzini refers in more than one passage to the relation between olfactory stimulus and onset of headache (“capitis dolor”), in particular, when he deals with the illnesses of pharmacists, brewers, tobacco workers, oil producers and carpenters. In the chapter, *Of the diseases of pharmacists*, an excellent description of osmophobia as a headache trigger is given: “I noticed that at times not only bad odours are harmful for the pharmacists, as in the preparation of an unguent of

dialthea, which causes nausea and vomiting to some, but also pleasant odours. In spring when they prepare infusions of roses for golden syrups, and when the whole shop smells of the rose beds of Paestum, I have heard some complain of severe headache, others of diarrhoea”.

Our data, derived from a study of 704 patients, of whom 569 were migraineurs (477 suffering from migraine without aura, 92 from migraine with aura) and 135 were diagnosed with tension-type headache, show that more than 40% of migraine patients refer osmophobia during an attack, while none of the patients with tension-type headache complain of this disturbance. Thus, osmophobia can be considered a highly specific symptom of migraine, of great importance in the differential diagnosis with tension-type headache.

Now, at the end of the present outline, the title “Padua, the cradle of modern medicine”, which is precisely the attribute given by the renowned medical historian, Henry Sigerist, to our Medical School, should not seem too ambitious.

In the *Taming of the Shrew*, William Shakespeare has one of his characters express “the grand desire to see fair Padua, nursery of the arts”. I am sure that the unique atmosphere that one feels not only between these ancient walls but also by simply walking in Padua, in its streets and under its arches, which have seen so many great contributors to the key developments of medical thinking, will provide our intellect and soul with an intense emotion that will enrich our experimental and clinical work.

Our medical school is today a very large one, enrolling more than two thousand pupils, and competing at an international level. All of this comes to us from a long, rich tradition, a cultural heritage that we are deeply proud of. We endeavour to pass down to the new generations, to our students, the illustrious, precious legacy of the Paduan Medical School, in order to foster their criticism in clinical judgement and their commitment in everyday practice.

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## Headaches in pregnancy

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**Abstract** Most women with migraine improve during pregnancy. Some women have their first attack. Migraine often recurs postpartum and can begin for the first time. Drugs are commonly used during pregnancy despite insufficient knowledge about their effects on the growing fetus. Most drugs are not teratogenic. Adverse effects, such as spontaneous abortion, developmental defects and various postnatal effects depend on the dose and route of administration and the tim-

ing of the exposure relative to the period of foetal development. While medication use should be limited, it is not absolutely contraindicated in pregnancy. Nonpharmacologic treatment is the ideal solution; however, analgesics such as acetaminophen and opioids can be used on a limited basis. Preventive therapy is a last resort.

**Key words** Migraine • Pregnancy • Acute • Preventive • Prophylaxis

### Drugs and pregnancy

Most drugs cross the placenta and have the potential to adversely affect the fetus, and, although studies have not absolutely established the safety of any medication during pregnancy, some are believed to be relatively safe [1]. Adverse drug effects depend on the dose and route of administration, concomitant exposures and the timing of the exposure relative to the period of development. Death to the conceptus, teratogenicity, foetal growth abnormalities, perinatal effects, postnatal developmental abnormalities, delayed oncogenesis, and functional and behavioural changes can result from drugs or other agents (Table 1) [2].

The FDA has five categories of labelling for drug use in pregnancy [3–5]. An alternate rating system is TERIS, an automated teratogen information resource wherein the rating for each drug or agent is based on a consensus of

expert opinion and the literature [6]. The FDA categories have little, if any, correlation to the TERIS teratogenic risk. This discrepancy results in part from the fact that the FDA categories were designed to provide therapeutic guidance and the TERIS ratings are useful for estimating the teratogenic risks of a drug and not *vice versa* [7].

### Headache treatment

The major concerns in the management of the pregnant patient are the effects of both the medication and the disease on the fetus. Because of the possible risk of injury to the fetus, medication use should be limited; however, it is not contraindicated during pregnancy [4, 8]. Because migraine usually improves after the first trimester, many women can manage their headaches with this reassurance

**Table 1** Definitions and drug effects

Spontaneous abortion	Death of the conceptus. Most due to chromosomal abnormality
Embryotoxicity	The ability of drugs to kill the developing embryo
Congenital anomalies	Deviation from normal morphology or function
Teratogenicity	The ability of an exogenous agent to produce a permanent abnormality of structure or function in an organism exposed during embryogenesis or fetal life
Fetal effects	Growth retardation, abnormal histogenesis (also congenital abnormalities and fetal death) The main outcome of fetal drug toxicity during the second and third trimesters of pregnancy
Perinatal effects	Effects on uterine contraction, neonatal withdrawal or haemostasis
Postnatal effects	Drugs may have delayed long-term effects: delayed oncogenesis, and functional and behavioural abnormalities

and nonpharmacologic means of coping, such as ice, massage and biofeedback [4, 9]. Some women, however, will continue to have severe, intractable headaches, sometimes associated with nausea, vomiting and possible dehydration. These conditions may pose a risk to the fetus that is greater than the potential risk of the medications used to treat the pregnant patient [8, 9].

Symptomatic treatment, designed to reduce the severity and duration of symptoms, is used to treat an acute headache attack. Individual attacks should be treated with rest, reassurance and ice packs. Symptomatic drugs are indicated for headaches that do not respond to nonpharmacologic treatment. The NSAIDs, acetaminophen (alone or with codeine), codeine alone or other opioids can be used during pregnancy [10]. Aspirin in low intermittent doses is not a significant teratogenic risk, although large doses, especially if taken near term, may be associated with maternal and fetal bleeding. Aspirin use should probably be reserved unless there is a definite therapeutic need for it (other than headache). In general, NSAIDs may be safely taken for pain during the first trimester of pregnancy. However, their use should be limited during later pregnancy, as some NSAIDs may constrict or close the fetal ductus arteriosus [10]. Barbiturate and benzodiazepine use should be limited. Ergotamine, dihydroergotamine (DHE) and triptans should be avoided [4, 9]. However, Reiff-Eldridge et al. [11] recently reviewed the Glaxo-Wellcome pregnancy registries and found that sumatriptan did not provide a risk estimate exceeding that expected in the disorder treated, and no pattern of defects has been observed.

The associated symptoms of migraine, such as nausea and vomiting, can be as disabling as the headache pain itself. In addition, some medications that are used to treat migraine can produce nausea. Metoclopramide, which decreases the gastric atony seen with migraine and enhances the absorption of coadministered medications, is extremely useful in migraine treatment [12]. Mild nausea can be treated with phosphorylated carbohydrate solution

(emetrol) or doxylamine succinate and vitamin B6 (pyridoxine) [10, 12]. More severe nausea may require the use of injections or suppositories. Trimethobenzamide, chlorpromazine, prochlorperazine and promethazine are available orally, parenterally and as a suppository, and can all be used safely. We frequently use promethazine and prochlorperazine suppositories. Corticosteroids can be utilised occasionally. Some use prednisone in preference to dexamethasone (which crosses the placenta more readily). Domperidone is an antiemetic used outside the United States. In the United Kingdom [13] its use is not advised during pregnancy, because of variable embryotoxic effects in animal tests. Severe acute attacks of migraine should be treated aggressively. We start IV fluids for hydration and then use prochlorperazine 10 mg IV to control both nausea and head pain. IV opioids or IV corticosteroids can supplement this.

### Preventive treatment

Increased frequency and severity of migraine associated with nausea and vomiting may justify the use of daily prophylactic medication. This treatment option should be a last resort. Preventive therapy is designed to reduce the frequency and severity of headache attacks. Prophylaxis should be considered when patients experience at least three or four prolonged, severe attacks a month that are particularly incapacitating or unresponsive to symptomatic therapy and may result in dehydration and fetal distress [9, 14]. Beta-adrenergic blockers such as propranolol have been used under these circumstances, although adverse effects, including intrauterine growth retardation, have been reported [10, 12, 14]. If the patient has a coexistent illness that requires treatment, one drug that will treat both disorders should be chosen. For example, propranolol [10] can be used to treat hypertension and migraine while fluoxetine can be used to treat comorbid depression.

## Drug exposure

If a woman inadvertently takes a drug while she is pregnant or becomes pregnant while taking a drug, determine the dose, timing and duration of the exposure(s). Ascertain the patient's past and present state of health and the presence of mental retardation or chromosomal abnormalities in the family. Using a reliable source of information (such as TERIS), determine if the drug is a known teratogen (although for many drugs this is not possible) [3, 6].

If the drug is teratogenic or the risk is unknown,

have the obstetrician confirm the gestational age by ultrasound. If the exposure occurred during embryogenesis, then high-resolution ultrasound can be performed to determine whether damage to specific organ systems or structures has occurred. If the high-resolution ultrasound is normal, it is reasonable to reassure the patient that the gross fetal structure is normal (within the 90% sensitivity of the study). However, fetal ultrasound cannot exclude minor anomalies or guarantee the birth of a normal child. Delays in achieving developmental milestones, including cognitive development, are potential risks that cannot be predicted or diagnosed prena-

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## Chronic headaches: from research to clinical practice

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**Abstract** Chronic daily headache (CDH) is a heterogeneous group of headaches that includes primary and secondary varieties. Primary CDH is a frequent entity that probably affects 4–5% of the population. It can be subdivided into headaches of short duration (<4 h/attack) like chronic cluster headache, and disorders of long duration (>4 h/attack). Primary CDH of long duration includes transformed migraine, chronic tension-type headache, and new daily

persistent headache and hemicrania continua. Analgesics, ergots and triptan overuse are frequent in all types of CDH. We revise recent insights into the epidemiology, pathophysiology, clinical characteristics and prognosis of CDH.

**Key words** Chronic migraine • Chronic tension-type headache • New persistent daily headache • Pathophysiology • Epidemiology

### Introduction

When we consider chronic daily headache (CDH), we refer to a heterogeneous group of headaches whose common characteristic is its chronicity. There is consensus to use the term “chronic daily headache” to refer to headaches occurring 15 or more days per month, including those associated with medication overuse.

### Epidemiology

The first population-based studies on CDH have been published in recent years [1, 2]. In these population-based sur-

veys, primary CDH occurs in approximately 4%–5% of the general population (Spain 4.7%, US 4.1% and China (elderly) 3.9%). In population samples, chronic tension-type headache (CTTH) is the leading cause of primary CDH with a one-year period estimated prevalence of 2.2% in Spain and in the United States, and 2.7% in China [1]. Epidemiological data are different when analysing the distribution of CDH patients that account for consultation in headache clinics. In subspecialty practices, CDH evolves from an episodic headache disorder in over 92% of cases, usually migraine (72% of cases), and from episodic tension-type headache (ETTH) in only 20% of the patients. CDH appears without history of previous headache and is unremitting from onset in about 8% of cases (NDPH). In headache clinic groups, the proportion of women is even higher with a female-male ratio of 4.6:1 [3].

## Pathophysiology

Different mechanisms are involved in the development of CDH. In these patients there is an altered central sensitisation which is manifested by increased spontaneous impulse discharges, increased responsiveness to noxious and non-noxious peripheral stimuli, and expanded receptive fields of nociceptive neurons. Migraine patients evolve a sensitisation of the trigeminal nucleus caudalis neurons caused by frequent vascular input due to frequent attacks, which may explain the development of CDH [4]. The enhanced neuronal responses represent a state of central sensitisation and, in addition, the cardiovascular response threshold to facial and intracranial stimuli is reduced, representing a state of intracranial hypersensitivity and cutaneous allodynia [5]. Migraine patients who had allodynia ipsilateral to the headache were significantly older than those who did not, hinting at a possible correlation between age and sensitisation. These findings provide a neural basis for the pathophysiology of migraine pain and suggest a basis for continued head pain.

In CTTH a central sensitisation appears, generated by prolonged nociceptive input from the periphery, particularly from myofascial tissues. Nitric oxide (NO) is involved in the development of this central sensitisation and it has been recently demonstrated that NO synthase inhibition has an analgesic effect in CTTH patients; this effect could be related to reduction in muscle hardness that could cause succeeding reduction of central sensitisation [6].

A down-regulation or suppression of an already partly suppressed or abnormal antinociceptive system also appears, particularly in individuals with analgesic overuse. The “rebound headache” does not appear in non-headache sufferers who use daily analgesics for another ailment such as arthritis pain, expressing an inherent vulnerability in the primary headache population that predisposes them to drug-induced headache.

Genetic factors should be considered in CDH. The genetic vulnerability of primary headaches is well known and has been demonstrated in a number of CDH patients [7].

## Imaging

One very interesting paper has shown, using a special MRI sequence, that iron homeostasis in the periaqueductal grey matter (PAG) was progressively impaired in patients with chronic or frequent migraine and possibly caused by repeated migraine attacks. These results emphasise the possible role of changes in the central pain structures as a possible cause of pain chronification [8].

## Comorbidity

Anxiety, depression, sleep disturbances and medication abuse are frequent in patients with CDH. In headache sufferers there is a correlation between high headache attack frequency, a long history of headaches and female sex, and rating elevation for both anxiety and depression. Patients with CDH show increased anxiety levels in all, and hysteric traits in some. With time, they may develop a depressive disorder.

## Drug overuse

Drug abuse is frequent in CDH patients. Different mechanisms probably contribute to its development. Psychological factors include the reinforcing properties of pain relief by drug consumption, a very powerful component of positive conditioning. Withdrawal headache is an additional problem, because whenever the patient tries to stop or reduce the medication, he experiences a worsening of the headache. Analgesic drugs also have psychotropic side effects such as sedation or euphoria that may stimulate drug dependency [9].

The actual dose limits and time needed to develop rebound headaches have not been defined in rigorous studies, but there is a consensus of the approximate doses [10].

Patients can overuse analgesics, ergots and opioids. In recent years, triptans have shown they could lead to drug-induced headache in patients with or without a previous history of analgesic overuse. The weekly dosages and the time of onset necessary to initiate triptan misuse-induced headache may be lower with the newer centrally penetrant triptans than with ergots or sumatriptan. The alarm sign of overuse is the progressive increase of attack frequency.

## Clinical presentation

CDH comprises a heterogeneous group of headaches whose common characteristic is their chronicity. The term “chronic daily headache” only refers to the frequency of headache that appears 15 or more days per month, including those associated with medication overuse.

### Chronic migraine

Following the last IHS classification, chronic migraine is a migraine headache occurring on 15 or more days per

month for more than 3 months in the absence of medication overuse [10]. This is a very restricted definition and the number of the patients fulfilling this criteria is low. The majority of patients suffering frequent migraines are patients that usually have a past history of episodic migraine of more than 15–20 years of evolution, that typically began in their teens or 20s. As the headaches increase in frequency over months or years, the associated symptoms of nausea, photophobia and phonophobia become less severe and less frequent. Headache may have clinical characteristics of migraine or of tension-type headache (TTH). When the migraine attack appears, it has less associated symptoms. Other migraine features may persist. Familial history of migraine is often present. Patients often continue to have typical migraine attacks, but in some cases their migraine headaches disappear completely. Usually it develops in the setting of analgesic overuse, but in 20%–30% of cases it may occur without it. Patients with medication overuse have a constant low-grade headache, which is aggravated hours after the use of the substance, and only partially alleviated with the consumption of repeated doses of medication. These CDH patients have a significant impairment of their health-related quality of life [11].

#### Chronic tension-type headache

CDH may also develop in patients who have a history of ETTH. Headache is more often diffuse or bilateral, frequently involving the posterior aspect of the head and neck. These patients do not have migraine features or previous or coexistent episodic migraine. Some mild associated symptoms, such as mild nausea, photophobia or phonophobia may be compatible with the diagnosis of

CTTH. It may also appear associated with or without medication overuse.

In population-based studies, CTTH appears to be the most frequent type of daily headache, even though little is known about its nature and what the syndrome actually represents. Some recent studies support that, at least in some part, CTTH is a disorder of the central nervous system with probable sensitisation of second-order trigeminal neurons and some peripheral component [12]. It has also been suggested that genetic factors influence the risk of CTTH [8]. But other causes of non-genetic familial aggregation or gene-environmental interactions may influence these findings.

#### New daily persistent headache

Patients with NDPH develop it in the absence of a previous history of episodic migraine or ETTH [10]. It is a rare type of CDH in which the onset of headache is usually abrupt, occurring in a few days. Some patients remember the exact day the headache started. These patients are generally younger than those with other types of CDH, so the proportion of patients diagnosed with NDPH is much higher in children and adolescent CDH series than in adults [13].

Commonly headache is similar to TTH, but there is no progressive evolution from a previous headache. NDPH is likely to be a very heterogeneous disorder. It has been related to a post-viral syndrome or to an unknown chronic infection [13]. In our personal experience, even when some patients referred an infection previous to the development of the headache, we could not serologically demonstrate it.

NDPH has been included in the new classification under the chapter of Other primary headaches.

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## Genetic risk factors in primary paediatric versus adult headache: complexities and problematics

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**Abstract** Numerous candidate genes for migraine have been proposed on the basis of their possible functional role in its pathogenesis. Genetic polymorphisms have been evaluated in association studies, some of which have been suggested to be susceptibility markers for adult migraine. To date, however, none of the identified polymorphisms in adult migraine susceptibility have been investigated in children, raising the possibility that they may not be necessarily involved in paediatric migraine susceptibility. This paper reviews studies of the genetic basis of migraine and summarises our experience in genetic association studies in primary paediatric headache susceptibility.

**Key words** Paediatric migraine • Susceptibility • Polymorphism • Endothelin type A receptor

### Introduction

Recurring primary headaches, such as migraine or tension-type, are common during childhood (2.5%) and adolescence (15%) [1]. However, while ever increasing evidence shows that migraine is a complex neurovascular disorder with genetic factors playing a primary role in its aetiology, none of the genetic factors which have to date been shown to be linked to adult migraine susceptibility have been investigated in children, for whom primary

headaches represent frequent causes for referral for neurologic assessment. In addition, while epidemiological, twin and family studies have revealed that approximately one-half of its variation is attributable to additive genes, with a negligible contribution of nonadditive genetic effects [2], the identification and validation of the underlying genetic risk factors poses enormous challenges even in adult migraine. The severity of migraine symptoms, such as the recurrence and duration of attacks and the age of onset, are variable among patients, thus rendering difficult both the definition of the appropriate phenotype as

well as the selection of the best population in which to investigate the genetic load. Furthermore, some individuals may, independently of the presence or absence of environmental influences or type of prophylactic therapy undertaken, remain attack-free despite their genetic load, while others will continue to suffer.

Given all this, the aim of the present paper is to provide a short overview of the current status of genetic susceptibility studies in migraine, herein including the problems involved in their application in paediatric *vs.* adult settings.

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### Genetic factors contribute to migraine

Genetic epidemiological studies of migraine show both positive family history and increased disease risk in relatives of migraine probands [3], the likelihood of which increases when the age at onset in the proband is below 20 years [4]. However, while familiarity supports the importance of genetic factors in migraine susceptibility, it does not prove heritability as it does not exclude the influences of shared environmental factors and common lifestyles. The significantly higher pairwise concordance rate among monozygotic compared to dizygotic twin pairs better supports the importance of genetic factors with heritability estimates of about 50% for migraine without aura and with aura [5]. In the case of tension-type headache, the genetic factor may have a major role in the aetiopathogenesis of chronic tension-type headache, whereas environmental influence is stronger in episodic tension-type headache [6].

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### Molecular studies of the genetic factors in adult migraine

Genome-wide scanning approaches have identified migraine susceptibility loci on chromosomes 1, 4, 6, 11, 14, 19 and X [7]. By investigating familial hemiplegic migraine (FHM), a rare Mendelian form of migraine with aura transmitted by autosomal dominance [8], the identification of migraine genes such as the calcium channel gene CACNA1A [9] and the  $\alpha 2$  subunit of the Na<sup>+</sup>/K<sup>+</sup> ATPase ATP1A2 gene [10, 11] was facilitated. In addition, given the major statistical power to detect several genes of small effect of the association studies by a candidate-gene approach, the relationship between migraine and candidate genes involved in pathogenic theories has been repeatedly investigated in adults [12]: unfortunately, the results have not often been replicated in subsequent, independent studies.

### Do the genes identified in the adult migraine susceptibility explain susceptibility in children? Our experience

Given the increased familial risk in relatives of migraine probands, we have, among the genes shown to be associated to adult migraine liability, recently focused on whether the -231 G>A polymorphism in the endothelin 1 type A receptor (EDNRA) shown to strongly modulate the risk of adult migraine [13] contributes to paediatric migraine susceptibility. Results to date obtained, however, show that the -231 G>A polymorphism in the EDNRA gene is neither associated with primary juvenile headache nor significantly correlated with main clinical features characteristic of the headache pathology, thus suggesting the possibility of an age-related interaction of the EDNRA polymorphic variant on migraine liability and disease expression [14].

Worth noting is that the only other published study tackling the genetic aspects of juvenile migraine has, based on evidence suggestive of an association between migraine and prothrombotic genetic risk factors, considered the factor V Leiden mutation [15] due to its high prevalence in patients with stroke and history of migraine [16]. As in our experience, no difference in the prevalence of this mutation was found in children and adolescents with migraine with aura *vs.* controls.

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### Conclusive considerations

As migraine is characterised by wide phenotypic and, most likely, genotypic heterogeneity, the identification and validation of the genetic risk factors involved critically depends on the accuracy of the determination of the disease phenotype. However, although the recently revised International Headache Society criteria (ICHD-II) have incorporated many developmentally related sensitive changes allowing for broader applicability in juvenile patients [17], the lack of specific clinical and biological markers reduce the possibility to differentially classify paediatric patients and, hence, the chance to identify the genetic risk factors involved. This complexity, in addition, further increases when considering the likelihood, of effects of “modifying” genes, as well as of co-morbidity, including phenotypical heterochronia, together with the possibility that the expression of the disease may vary as a function of age. Thus, whilst the heterogeneous complex traits of migraine may, in part, account for the current discrepancies in genetic susceptibility studies conducted in adult and paediatric migraineurs, other factors including comorbidity of migraine with other age-related disorders sharing common similar pathways may be involved [18, 19], while environmental and individually related factors may interact to raise the disease expression.

In sum, although the identification and validation of the genetic risk factors in primary headache susceptibility introduce the possibility of identifying groups of patients who possess particular diagnostic or prognostic characteristics, it is particularly important to identify if and how these advances apply in different clinical settings, herein including the paediatric and adolescent settings, through the design of appropriate clinical trials. Only in this way

it will be possible, at least on the basis of our attempts to identify genetic susceptibility markers in primary paediatric headache susceptibility based on those shown to be associated to adult migraine liability, to ensure that the resulting data are sufficiently robust in order to inform clinical decision making and to revise the available treatment strategies in primary headache disorders arising in either the paediatric or adult stage.

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## Functional serotonin 5-HTTLPR polymorphism is a risk factor for migraine with aura

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**Abstract** In the present work, we report that the functional serotonin transporter gene promoter (5-HTTLPR) polymorphism is involved in migraine pathogenesis. The distribution of 5-HTTLPR genotypes was significantly different in MA patients (S/S vs. S/L vs. L/L=32.7 vs. 42.3 vs. 25.0%), MO patients (18.5 vs. 39.1 vs. 42.4%) and CON (18.0 vs. 51.3 vs. 30.7%; chi-square test,  $p<0.05$ ). In 5-HTTLPR S/S carriers, the odds ratio for MA risk was 2.60 (95% confidence interval [95%CI]=1.75–3.85) compared to CON, and it was 2.14 (95%CI=1.42–3.21) compared to MO. These data provide a further

insight on the complex genotype-phenotype relationship involved in MA pathogenesis, and might eventually result in new and individualised prognostic and therapeutic measures.

**Key words** 5-HTTLPR • Serotonin • Polymorphism • Migraine • Aura

### Introduction

It has been reported that genetic background linked to serotonin (5-HT) metabolism is involved in migraine pathogenesis. Indeed, the most effective drugs in acute migraine are the triptans, highly selective 5-HT<sub>1B/1D</sub> agonists.

There is evidence that 5-HT activity is regulated by a functional polymorphism within the promoter region of the 5-HT transporter gene (5-HTT gene-linked promoter region, 5-HTTLPR) [1]. The 5-HTTLPR provides the primary mechanism for reuptake of 5-HT after its release into the synaptic cleft and is thus critical to the maintenance of brain 5-HT homeostasis.

*In vitro* studies evidenced that the basal activity of 5-HTTLPR allele with a 44-base pair insertion (long variant, L) leads to nearly twice as much 5-HTT transcription compared to the other allele (short variant, S) [2].

Different studies investigated the role of genetic variations of 5-HT receptors as risk factors for migraine, their role being still not completely understood [3–5]. A recent work suggested a link between 5-HTTLPR polymorphism and migraine with aura [6].

In the current study, we further evaluate the role of functional 5-HTTLPR polymorphism as a risk factor for migraine.

## Methods

### Subjects

One hundred and forty-four consecutive migraine patients and 105 nonheadache unrelated healthy volunteers were enrolled at Headache Centres of University of Brescia and "Città di Brescia" Hospital. All migraine patients and healthy controls were interviewed by an experienced neurologist. A standardised record of all demographic characteristics, family history for migraine, cerebrovascular disease, cardiovascular disease and neurological disorders was obtained. The presence of other comorbidities was also evaluated.

All subjects performed a clinical and neurological work-up, and a blood drawing for 5-HTTLPR genotyping.

The migraine patients were diagnosed as having migraine without aura (MO) or migraine with aura (MA) according to the International Headache Society (IHS) criteria [7].

The study was conducted in accordance with local clinical research regulations and informed consent was required from all the subjects.

Polymorphism analyses were performed blinded to diagnosis and genotype.

### 5-HTTLPR genotyping

Genomic DNA was prepared from 10 ml of blood using the salting out method. Primers 5'-GGCGTTGCCGCTCTGAATGC-3' and 5'-GAGGGACTGAGCTGG ACAACC-3' were used to assess GC-rich regions composed of 20–23 base pair (bp) repeating units in the 5-HTTLPR gene.

The 50- $\mu$ l reactions contained 50 nmol genomic DNA, 0.17 mmol/l each of dATP, dCTP and dTTP; 0.083 mmol/l of dGTP; 1.5 mmol/l MgCl<sub>2</sub>, 0.1  $\mu$ g of each primer, and 1 unit Taq polymerase. Following an initial denaturation step at 95°C for 3 min, DNA was amplified in 35 PCR cycles (95°C for 45 s; 66°C for 1 min; 72°C for 1 min); the final extension step was 72°C for 7 min.

A 15- $\mu$ l aliquot of PCR product was resolved on 2.5% agarose gel, and genotype was determined by fragments' size of 484 bp (short allele, S) or 528 bp (long allele, L).

### Statistical analysis

The Hardy-Weinberg equilibrium was verified for all tested populations. The differences in genotype frequencies and other risk factors were analysed by the  $\chi^2$  test. Demographic characteristics in the groups were compared by Student's *t*-test or one-way ANOVA and Bonferroni post-hoc analysis. Odds ratio (OR) and 95% confidence intervals (95% CI) were also calculated. Results were expressed as mean $\pm$ standard deviation (SD). The level of significance was taken at  $p < 0.05$ .

## Results

One hundred and forty-four migraine patients and 105 non-headache migraine subjects were enrolled. Migraine patients were classified into two subgroups according to the presence (MA,  $n=52$ ) or the absence (MO,  $n=92$ ) of

**Table 1** Demographic and clinical characteristics of migraine patients according to migraine subtypes and of nonheadache controls

Variable	CON	MO	MA	<i>p</i> *
<i>n</i>	105	92	52	–
Age, years	37.3 $\pm$ 7.7	35.1 $\pm$ 11.8	33.3 $\pm$ 9.9	n.s.
Gender, F%	79.4	80.2	78.8	–
Age at onset, years	–	20.0 $\pm$ 9.8	21.0 $\pm$ 9.5	–
FH migraine, %	8.7	75	77.8	0.0001
FH cerebrovascular disease, %	15.0	39.3	22.5	0.001
FH cardiovascular disease, %	22.3	40.4	22.5	0.02
FH neurological disease, %	9.5	8.3	2.5	n.s.
Smoking, %	18.8	25.8	19.6	n.s.
Hypertension, %	2.3	8.4	6.2	n.s.
Cardiomyopathy, %	1.6	1.2	12.5	0.001
Hypercholesterolaemia, %	0.0	21.4	19.2	0.0001
Dismetabolism, %	1.6	3.6	2.0	n.s.
Asthma, %	3.9	6.0	6.2	n.s.
Allergy, %	9.4	26.5	23.0	0.01
Head trauma, %	5.5	8.4	18.8	0.05
Epilepsy, %	1.5	1.2	4.1	n.s.
Gastritis/gastric disease, %	3.9	27.1	14.6	0.0001

CON, nonheadache unrelated healthy volunteers; MO, migraine patients without aura; MA, migraine patients with aura; F, female; FH, family history

\*Controls vs. MO vs. MA

aura. MA and MO subgroups did not differ for demographic characteristics, family history of migraine or other associated comorbidities.

Patients with migraine showed an increased incidence of allergies, previous head trauma, hypercholesterolaemia, gastritis or gastric disease, and cardiomyopathy compared to the control sample. Family history of migraine was more common in migraine patients than in nonheadache volunteers.

The distribution of 5-HTTLPR genotypes was significantly different in MA patients (S/S vs. S/L vs. L/L=32.7 vs. 42.3 vs. 25.0%), MO patients (18.5 vs. 39.1 vs. 42.4%) and CON (18.0 vs. 51.3 vs. 30.7%; chi-square test,  $p<0.05$ ).

5-HTTLPR S/S was found to be associated with MA, its incidence being higher in this group (32.7%) compared to CON (18.0%, chi-square test,  $p<0.05$ ) and to MO patients (18.5%,  $p<0.05$ ). No difference in demographic characteristics, i.e., gender or age at onset, family history of migraine and other associated comorbidities between 5-HTTLPR S/S and 5-HTTLPR non-S/S carriers was observed.

In 5-HTTLPR S/S carriers, the OR for MA risk was 2.60 (95%CI=1.75–3.85) compared to CON, and it was 2.14 (95%CI=1.42–3.21) compared to MO.

## Discussion

The relationship between the 5-HT pathway and migraine is well established. Thus, different studies have investigated a possible link between genetic background linked to 5-HT metabolism and migraine pathogenesis. It has been suggested that T102C polymorphism of 5-HT2A gene is a risk factor for migraine [3], and a recent work has supported the view that 5-HTTLPR genetic variation is related to migraine with aura [6].

Our results confirm and extend previous studies, and may have several implications for clinical practice. These data suggest that MA and MO have distinct genetic predisposing factors. Moreover, the well known role of this polymorphism on 5-HT transcription [2] may reflect a different response to 5-HT agonist drugs, such as triptans, whose migraine symptomatic effect is still unpredictable.

Further studies are required to elucidate the role of 5-HTTLPR polymorphism in migraine. Notwithstanding, these data provide a further insight on the complex genotype-phenotype relationship involved in migraine pathogenesis, and might eventually result in new and individualised prognostic and therapeutic measures.

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## Association between migraine and HLA-DRB1 gene polymorphisms

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**Abstract** We examined the distribution of *HLA-DRB1* alleles in a cohort of 255 Italian migraine patients and in a control group of 325 healthy subjects. The frequency of DRB1\*12 allele was found to be significantly reduced ( $p=0.02$ ) in patients with migraine while the DRB1\*16 allele was significantly increased ( $p=0.04$ ) in comparison with controls. When the patients were divided into disease subgroups (migraine with and without aura), HLA-DRB1\*\*16 allele was significantly increased ( $p<0.05$ ) only in migraine without aura patients. We conclude that, in Italian patients, migraine is associated with differ-

ent alleles of the HLA-DRB1 locus. Our data suggest the presence of a genetic susceptibility factor for migraine within the HLA region.

**Key words** HLA-DRB1 • Migraine • Aura • Major histocompatibility complex • MHC

### Introduction

Migraine is a chronic neurovascular disorder that, in Western countries, affects approximately 15% of the general population [1]. The aetiology of migraine is still unknown but several studies support a strong genetic basis for the disease [2]. Mutations in the *CACNA1A* and *ATP1A2* genes are associated with familial hemiplegic migraine, a rare subtype of migraine with aura [3, 4]. The genes involved in the more common form of migraine, like migraine with and without aura, are still unknown.

Epidemiological studies have shown the presence of a significant comorbidity between migraine and some diseases

related to the HLA system, like asthma and narcolepsy [5, 6]. This comorbidity suggests the presence, within the HLA region, of genetic factors involved in the disease pathogenesis.

Previous studies evaluating the relation between HLA system and migraine provided conflicting results [7, 8]. Recently, a significant association was found between migraine and polymorphisms of two genes, *TNF-alpha* and *TNF-beta*, located in the HLA Class III region [9, 10].

To further investigate this issue, we performed an association study between polymorphisms of the *HLA-DRB1* gene and migraine in a large cohort of Italian migraine patients. The purpose of this study was to assess whether *HLA-DRB1* alleles confer susceptibility to migraine or are related to specific clinical subgroups.

## Materials and methods

Two hundred and fifty-five consecutive migraine patients (77 males, 178 women; mean age $\pm$ SD=40.87 $\pm$ 13.10 years) attending the Headache Center of the University of Turin (Italy), were involved in the study. The diagnosis of migraine was made according to the International Classification of Headache Disorders (ICHD-II) criteria [11]. For additional analyses, migraine patients were divided into 2 subgroups: (A) migraine without aura (ICHD-II code 1.1), 214 patients (65 males, 149 females; mean age $\pm$ SD=41.5 $\pm$ 12.0 years); and (B) migraine with aura (ICHD-II code 1.2), 41 patients (12 males, 29 females; mean age $\pm$ SD=36.4 $\pm$ 13.6 years). A group of 325 age and geographically matched healthy subjects (151 males, 174 females, mean age $\pm$ SD=41.96 $\pm$ 14.86 years) served as control. The controls were blood donors and were screened by a neurologist specialised in headaches in order to exclude migraine and/or cluster headache. The protocol of this study was reviewed and approved by the Medical Ethics Committee of the San Giovanni Battista Hospital of Turin and written informed consent was obtained from all participants.

Genomic DNA was extracted from EDTA-treated blood using a commercial DNA extraction kit (QiAmp blood kit; Kagan, Crawley, UK). HLA-DRB1 typing was performed at the two-digit level by PCR amplification using specific probes and

primers (Dynal Biotech Ltd., Bromborough, Wirral, UK). The Hardy-Weinberg equilibrium was verified for all tested populations. Statistical analyses were performed using SigmaStat version 1.0 (Jandel Corp., 1994, San Rafael, CA). A level of  $p < 0.05$  was accepted as statistically significant.

## Results

Table 1 shows the distribution of *HLA-DRB1* alleles in migraine patients and controls. The phenotypic frequencies of *HLA-DRB1* alleles were similar to those previously found in the Italian population [12]. In patients with migraine, the frequency of the HLA-DRB1\*12 allele was found to be significantly lower than in controls ( $\chi^2=5.03$ ,  $p=0.025$ , OR: 0.28, 95% CI: 0.08–0.88). The frequency of HLA-DRB1\*16 was significantly higher ( $\chi^2=4.10$ ,  $p=0.043$ , OR: 1.80, 95% CI: 1.02–3.19) in migraine patients. No significant difference was found in the remaining alleles.

Table 2 shows the comparison of *HLA-DRB1* alleles between migraine subgroups and healthy controls. In

**Table 1** *HLA-DRB1* allele distribution in migraine patients and controls

Allele	Migraine patients (n=255)	Healthy controls (n=325)	p	OR (95% CI)
DRB1*01	42	58	0.74	
DRB1*03	38	52	0.81	
DRB1*04	46	58	0.96	
DRB1*07	52	82	0.24	
DRB1*08	11	16	0.88	
DRB1*09	1	1	0.59	
DRB1*10	11	5	0.08	
DRB1*11	136	174	0.98	
DRB1*12	4	18	0.025	0.28 (0.08–0.88)
DRB1*13	60	73	0.85	
DRB1*14	40	34	0.10	
DRB1*15	36	55	0.39	
DRB1*16	33	24	0.043	1.80 (1.02–3.19)

**Table 2** Comparison of *HLA-DRB1* allele distribution between controls and migraine subgroups

Allele	Migraine without aura (n=214)	Migraine with aura (n=41)
DRB1*01	0.75	0.93
DRB1*03	0.84	0.99
DRB1*04	0.96	0.69
DRB1*07	0.23	0.81
DRB1*08	0.66	0.78
DRB1*09	0.67	0.22
DRB1*10	0.11	0.39
DRB1*11	0.83	0.42
DRB1*12	0.06	0.25
DRB1*13	0.99	0.69
DRB1*14	0.05	0.90
DRB1*15	0.18	0.36
DRB1*16	0.02*	0.77

\*OR: 1.97; 95% CI: 1.10<OR<3.54

migraine without aura patients, the frequency of the \*16 allele was significantly ( $\chi^2=5.35$ ,  $p=0.045$ , OR: 1.97, 95% CI: 1.10–3.54) increased in comparison with controls. No significant difference in HLA-DRB1 allele distribution was found in the remaining subgroups.

## Discussion

Our study shows the presence of a significant association between alleles of the *HLA-DRB1* gene and migraine. Subjects carrying the \*12 allele of this gene present a significant reduction in the risk for migraine, suggesting a protective role for the disease. On the contrary, the carriage of the \*16 allele is associated with a two-fold increase in disease risk. When the migraine patients were divided into subgroups (migraine with and without aura), only migraine without aura patients presented a significant increase of the

\*16 allele. These alleles may be considered as risk factors for migraine without aura in the Italian population. In a previous study, Martelletti et al. [13] genotyped 45 migraine patients for *HLA-DRB1* alleles and found no significant difference with controls. The number of patients examined in this study was probably too low for the detection of a statistically significant difference.

The most likely explanation of our data is that the *DRB1* locus is in linkage disequilibrium (LD) with other genetic polymorphisms which are responsible for this association. The *DRB1* gene is located on chromosome 6p21, within the HLA-Class III region, and this region is characterised by a high LD [14]. Further studies, using different methods for HLA analysis, are needed to confirm the presence of susceptibility genes for migraine in this genomic region.

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## Cytotoxic T lymphocyte antigen 4 polymorphism 49 (A>G) and migraine

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**Abstract** Migraine without aura (MO) and migraine with aura (MA) are disorders involving multiple environmental and genetic factors. The A/G polymorphism located within exon 1 of the gene encoding the cytotoxic T lymphocyte antigen 4 (CTLA-4) is associated with several HLA-associated multifactorial diseases. The CTLA-4 family shows a negative control on T-cell proliferation and cytokine production (TNF- $\alpha$  and IL-10). In the present study we investigated the contribution of the candidate gene CTLA-4 in migraine pathophysiology. Included in the study were 96 MO and 39 MA migraine patients and 106 healthy individuals as control group. The results showed no statistical difference of allele frequencies between patient group and control group. These results would indicate no association between MA and MO migraine and CTLA-4 polymorphism, excluding any possible role of the CTLA-4 gene as a

genetic factor determining susceptibility to migraine.

**Key words** Candidate gene • Migraine • CTLA-4 • Polymorphism

### Introduction

In the past decade increasing attention has been given to the study of migraine. Migraine is a recurring headache disorder manifest in attacks lasting 4–72 h and affecting

about 10% of the general population. Migraine is clinically distinguishable as two main types: migraine with aura (MA) and migraine without aura (MO), i.e., with or without the complex of focal neurological symptoms (scotomas, scintillations, fortification spectra, etc.) that initiates or accompanies pain attacks [1].

The two types of migraine involve multiple environmental and genetic factors. Several studies on familial hemiplegic migraine (FHM), a rare autosomal dominant subtype of MA, identified the responsible genes on chromosome 19 and chromosome 1 [2]. In two previous studies, we hypothesised both a protective role for the HLA-DR2 antigen, providing an additional basis for the proposed genetic heterogeneity between migraine without aura and migraine with aura, and involvement of lymphotoxin a (TNF- $\beta$ ) as a susceptibility gene in migraine without aura [3, 4]. The A/G polymorphism located within exon 1 at position 49 of the gene encoding the cytotoxic T lymphocyte antigen 4 (CTLA-4) is associated with several multifactorial HLA-associated diseases such as type 1 diabetes, inflammatory bowel diseases, etc. The CTLA-4 family shows a negative control on T-cell proliferation and cytokine production (TNF- $\alpha$  and IL-10) [5, 6]. In the present study we searched for an association between migraine and the gene encoding CTLA-4.

## Material and methods

### Patients and controls

A controlled study was done in 135 migraine patients: 39 with MA (9 males, 30 females, mean age  $39.7 \pm 7.4$ ) and 96 with MO (21 males, 75 females, mean age  $36.7 \pm 6.9$ ) diagnosed according to the 2004 International Headache Society (IHS) criteria. One hundred and six unrelated healthy and migraine-free subjects from the same geographic area (Central Italy), randomly selected, were used as controls. The study protocol was approved by our institutional ethics board and informed consent was obtained from all patients and from controls. The recommended principles of the Declaration of Helsinki, September 1989, were closely observed during this clinical research study.

**Table 1** CTLA-4 allele frequencies in MA and MO patients and controls

CTLA-4 alleles	Controls ( $n=106$ )		MA ( $n=39$ )		MO ( $n=96$ )	
	<i>n</i>	Frequency	<i>n</i>	Frequency	<i>n</i>	Frequency
A	150	0.7075	51	0.6538	121	0.6302
G	62	0.2925	27	0.3462	71	0.3698

**Table 2** CTLA-4 allele frequencies in migraine and controls

CTLA-4 alleles	Controls ( $n=106$ )		Patients ( $n=135$ )	
	<i>n</i>	Frequency	<i>n</i>	Frequency
A	150	0.7075	172	0.6370
G	62	0.2925	98	0.3630

## Methods

Genomic DNA was isolated from proteinase-K-treated peripheral blood leukocytes according to the salting-out method. The PCR-RFLP BstEII polymorphism of the CTLA-4 gene was studied by PCR amplification using specific primers previously described by Marron et al. [5] of a 152-bp fragment in the first exon of the gene, subsequently digested by BstEII restriction enzyme. The presence or absence of the restriction site defines two alleles: CTLA-4 A results in a cleaved fragment of 130 bp and CTLA-4 G allele yields an intact 152-bp fragment. Digested products were separated by electrophoresis on 3.5% agarose gel.

## Statistics

CTLA-4 allele frequencies were estimated by direct counting in patients and controls. The frequencies of alleles or genotypes of patients and controls were compared by chi-square contingency table analysis. Differences were considered statistically significant when  $p$  was less than 0.05. Hardy-Weinberg equilibrium at CTLA-4 locus was verified in patients and control populations.

## Results

Allele distribution of the studied polymorphism is in Hardy-Weinberg equilibrium in both controls and patients (data not shown). No significant CTLA-4 associations either with MO or with MA were found and when we compared the whole group of patients with controls (Tables 1, 2). The distribution of CTLA-4 genotypes in migraine patients and controls are shown in Table 3. No significant differences were observed between patients and controls.

**Table 3** Distribution of CTLA-4 genotypes in MA and MO patients and controls

CTLA-4 alleles	Controls (n=106)		MA (n=39)		MO (n=96)	
	n	Frequency	n	Frequency	n	Frequency
A-A	51	0.481	14	0.359	35	0.365
A-G	48	0.453	23	0.590	51	0.531
G-G	7	0.066	2	0.051	10	0.104

## Discussion

In previous studies, we observed an involvement of the HLA polymorphism and TNF- $\beta$  in susceptibility to migraine. In addition we have to look for other susceptibility candidate genes located either in the same region or on other chromosomes. The region 2q33, where the CTLA-4 gene is located, is considered to be associated with several multifactorial diseases.

To the best of our knowledge, this study is the largest ever conducted on the relationship between migraine subjects and CTLA-4 49 A>G polymorphism in the Italian population. It indicates that there is no association between migraine and CTLA-4 polymorphism. This suggests that CTLA-4 polymorphism does not impact on the risk of developing of migraine. As several genetic factors are involved in multifactorial diseases, further studies are needed to identify other genes responsible for genetic susceptibility in migraine.

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## Neurophysiological approach to central pain modulation in primary headaches

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**Abstract** The study of CNS pain-modulating pathways has led to important discoveries about the role of central nociceptive structures such as PAG and hypothalamus in the pathophysiology of episodic and chronic primary headaches. Functional neuroimaging studies have revealed that primary headaches are characterised by different patterns of activation of central pain modulatory structures. A future model of headache pathophysiology investigating the contribution of CNS pain-modulating pathways will probably increase our understanding of pain processing in primary headaches. Herein we review the neurophysiological approaches to assess central pain modulation in primary headaches with emphasis on the diffuse noxious inhibitory control, a form of endogenous pain inhibition. In addition, patients' data will be pre-

sented that highlights the utility of such methods for primary headache's pathophysiology and clinical monitoring.

**Key words** Headache • Neurophysiology • DNIC • Central pain modulation

### Introduction

Progress in pain research has definitively established that pain is not automatically transmitted from the periphery to the brain. The pain signalling system consists of several channels with many synaptic relays, feedback circuits and

a high degree of plasticity. From the first synapse the pain signal is under a powerful modulatory control adapting pain perception to the external and internal environmental needs.

The study of CNS pain-modulating pathways has led to important discoveries about the role of central nociceptive structures such as PAG and hypothalamus in the patho-

physiology of episodic and chronic primary headaches [1]. Functional neuroimaging studies have revealed that primary headaches are characterised by different patterns of activation of central pain modulatory structures [2]. A future model of headache pathophysiology investigating the contribution of CNS pain-modulating pathways will probably increase our understanding of pain processing in primary headaches resulting in a corresponding improvement of our ability to treat it and even prevent it. We will review the neurophysiological approaches to assess central pain modulation in primary headaches with emphasis on diffuse noxious inhibitory control (DNIC), a form of endogenous pain inhibition. In addition, patients' data will be presented that highlights the utility of such methods for primary headache's pathophysiology and clinical monitoring.

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### **Descending control of pain. Diffuse noxious inhibitory control**

Pain descending modulatory pathways represent a complex network of supraspinal structures operating with both direct and indirect facilitatory and inhibitory pathways on spinal cord and trigeminal primary nociceptive afferents [3]. The physiological role of these systems is to potentiate or suppress nociceptive messages to the brain as a function of internal and external environments of the organism. Supraspinal pain modulation may be dynamically investigated by examining the diffuse noxious inhibitory control (DNIC) [4]. DNIC may be defined as the inhibition of nociceptive neurons in the spinal and trigeminal dorsal horns produced by a noxious stimulus applied in any part of the body distant from the neuron's excitatory receptive field [4]. Anatomical and electrophysiological studies indicate that DNIC results from a complex spino-bulbo-spinal loop, specifically activated by A-delta and C peripheral fibres [4]. The brainstem, namely the medullary reticular formation, is the key neuronal link of the loop subserving DNICs. It has been shown that the RIII reflex as well as the perception of pain are strongly inhibited by DNIC systems [5]. There is a common opinion that the wide dynamic neurons are the principal site where the DNICs exert their inhibitory modulation. As such neurons are activated in unpredictable but permanent ways by all non-noxious and noxious stimuli, it has been postulated that the resulting "basic somesthetic activity" when transmitted to higher centres could constitute a "noise", from which these centres would have difficulty extracting a clear signal of pain. In this view, DNICs could provide the filter which would allow such an extraction to be achieved [4, 5].

Very recently Edwards et al. [6] have demonstrated that DNIC measurements are a consistent predictor of clinical pain and physical health highlighting the potential

clinical relevance of DNIC in the field of pain clinical neurophysiology. Accordingly, a dysfunction of DNIC mechanisms has been found in patients with different forms of chronic painful disorders [7, 8]. It has been supposed that a defective DNIC activity may induce a consequent facilitation of central sensitisation leading to chronic pain syndromes [7]. A recent study of our research group [9], which investigated in detail the inhibitory effect exerted by DNICs on the temporal summation of the RIII in humans, revealed a gender-specific inhibition of the temporal summation threshold of the RIII reflex in healthy subjects. These findings strongly support the notion that the supraspinal modulation of pain sensation and pain-related reflex effects prompted by DNICs are not limited to the inhibition of pain transmission, but may also be involved in regulating the development of the neuronal plasticity of nociceptive neurons. In the last few years we have performed several research studies with the aim of defining the pathogenetic role of pain-modulating systems subserving DNIC in primary headaches and their usefulness in clinical neurophysiology of the headache.

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### **DNICs in migraine and chronic tension-type headache patients**

DNIC was examined in 24 migraineurs without aura, 17 patients with chronic tension-type headache (CTTH) and 20 healthy subjects by means of nociceptive flexion RIII reflex and the cold pressor test (CPT) as heterotopic noxious conditioning stimulation (HNCS) [10]. The subjective pain thresholds (Tp) and the RIII reflex threshold (Tr) were significantly lower in CTTH vs. controls. In controls a significant inhibition of the RIII reflex was observed during CPT ( $-30\%$ ,  $p < 0.05$ ). Conversely, migraine and CTTH patients showed facilitation ( $+31\%$ ,  $p < 0.05$  and  $+40\%$ ,  $p < 0.01$ , respectively) of the RIII reflex during the HNCS. The present study demonstrates a dysfunction in systems subserving DNIC in headache patients. Our findings may be interpreted as the result of the prevalence of descending facilitatory influences activated in the setting of an acute noxious stimulation, such as CPT. We suggest that an impairment of endogenous supraspinal pain modulation systems may be an important common denominator in the pain mechanism of both CTTH and migraine. In the former, the increased facilitation and decreased inhibition of pain transmission at a brainstem level may be secondary to prolonged nociceptive inputs from peripheral myofascial tissues; in the latter, the same pattern of supraspinal pain modulation may be the result of a primary dysfunction of brainstem nuclei. Impairment of endogenous supraspinal pain modulation systems may

contribute to the development and/or maintenance of central sensitisation in primary headaches.

### Descending inhibitory control on nociceptive trigeminal-mediated responses in migraine with and without aura

We investigated the DNICs' function in the interictal period of 43 patients suffering from migraine without aura and with aura ( $n=11$ ) [11] by studying the trigemino-cervical (TCR) and the trigemino-spinal responses (TSR). Such reflexes have shown to be markedly inhibited by activation of the DNIC system by means of CPT [12]. The recovery curve of TCRs was significantly faster in migraine patients than in controls. The recovery curve of TSR was normal. Activation of the DNICs through the CPT significantly reduced the TCRs and TSRs area in both migraine patients and controls and the extent of this reduction did not differ significantly between migraineurs and controls (all  $p>0.05$ ). No correlation was found between TCR/TSR neurophysiological parameters and DNIC activity. These data suggest that migraine patients, in the interictal phase, are characterised by a specific, abnormal, interictal hyperexcitability of the neuronal substrate that mediates TCR whereas endogenous supraspinal pain modulation is activated similarly to normal subjects. These findings are contrasting with those reported before. These discrepancies may be explained by the use of different population of migraineurs and that the pain-induced motor responses recruitment in cranio-facial region is more variable than in other districts. From a theoretical point of view, DNIC activity could be related to specific migraine phenotypes such as the presence/absence of allodynic attacks, a hypothesis we are currently investigating.

### Effect of DNICs on temporal summation of the nociceptive flexion reflex in medication-overuse headache

The RIII reflex threshold (Th), and the RIII temporal summation threshold (TST) were investigated at baseline and during activation of DNIC in 23 patients diagnosed as having migraine+medication-overuse headache (MOH), and 20 healthy controls. MOH patients were examined before and after a standardised detoxification programme.

Before detoxification, a significantly lower RIII Th and TST were found in MOH *vs.* controls (mean values 9.78 *vs.* 15.4 and 8.6 *vs.* 13.2,  $p<0.01$ ); in these patients CPT induced a significantly ( $p<0.01$ ) lower TST increase and RIII inhibition compared with controls. The psychophysical results paralleled neurophysiological findings. After detoxification RIII TST and CPT effect on TST were normalised whereas RIII Th and CPT effect on RIII improved but remained significantly different from control values. These data suggest that MO-induced chronification of migraine determines a central sensitisation and an enhanced temporal integration of nociceptive stimuli alone with a hypofunction of DNIC. Such abnormalities are partially and differently reverted after detoxification.

### Conclusions

DNIC is a valuable neurophysiological method for investigating central pain modulation in primary headaches. Additional research is necessary to further our understanding of the pathophysiological role of DNIC in primary headaches and its contribution to the development or maintenance of central sensitisation.

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## Habituation of single CO<sub>2</sub> laser-evoked responses during interictal phase of migraine

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**Abstract** A reduced habituation of averaged laser-evoked potential (LEP) amplitudes was previously found in migraine patients. The aim of the present study was to assess the habituation of single LEP responses and pain sensation during the interictal phase in migraine patients. Fourteen migraine patients were compared with ten control subjects. The pain stimulus was laser pulses, generated by CO<sub>2</sub> laser, delivered to right supraorbital zone. Patients were evaluated during attack-free conditions. The LEP habituation was studied by measuring the changes of LEP amplitudes across and within three consecutive repetitions of 21 non-averaged tri-

als. In migraine patients the N2–P2 wave amplitudes did not show a tendency toward habituation across and, above all, within the three repetitions. Anomalous behaviour of nociceptive cortex during the interictal phase of migraine may predispose patients to headache occurrence and persistence.

**Key words** Migraine • Laser-evoked potentials • Habituation

### Introduction

The majority of studies on evoked and event-related potentials in migraine have shown two abnormalities: increased amplitudes of averages of large numbers of trials and lack of habituation in successive trial blocks during the pain-free phase, which seems to reverse to normal pattern for a homeostatic mechanism [1]. This pattern has suggested an abnormal state of cortical excitability during the interictal phase of migraine, which is reversed during the attack for a homeostatic mechanism [1]. Clinical neurophysiological studies have shown that infrared laser CO<sub>2</sub>, argon or thulium-YAG laser can be

used to generate an evoked potential that can be recorded from the vertex (late components) and temporal regions (early components) of the skull by selective activation of Adelta fibres (laser evoked potentials: LEPs) or C fibres (ultra-late LEPs) [2]. A reduced habituation pattern of the LEPs in response to repetitive noxious stimuli was found during the interictal phase of migraine, with respect to control subjects, according to the results obtained by the application of other event-related potentials [3]. The reduced habituation pattern seemed to involve mainly the vertex complex [3]. In a further study [4], we examined the behaviour of LEP amplitudes in three subsequent series of stimulation, which was correlated with the subjective pain sensation, during the non-symptomatic and

the acute phase of migraine. In controls, LEP amplitudes showed a progressive reduction in the three series, which corresponded to the decline of pain sensation. In migraine there was a clear reduction of habituation of both LEP amplitudes and pain sensation, during both the acute and the pain-free phase, with a loss of correlation between pain rating and LEP amplitudes, confirming abnormal behaviour of nociceptive cortex, which did not restore during migraine, differently from other modalities of sensory stimulation [1].

The averaging of the single responses within the single series may occult the development of habituation phenomena. It is known that a pattern of amplitude recovery after initial low-amplitude cortical responses during repetitive sensory stimulation causes reduced habituation, which may be a compensatory phenomenon of low pre-activation levels of sensory cortex [1, 5].

The aim of the present study was to perform further investigation of habituation phenomena to noxious stimuli in migraine, considering the single cortical responses within three consecutive series of CO<sub>2</sub> laser stimulation in a cohort of migraine patients during the pain-free phase compared with healthy controls.

## Methods

### Subjects

Fourteen migraine without aura patients, diagnosed on the basis of the IHS criteria (2004), were included in the study. They were 5 males and 9 females, aged 22–53. All patients were diagnosed after six months' follow-up. Patients with general medical, neurological or psychiatric diseases, and patients who were taking psychoactive drugs or prophylactic treatment for headache, or who were assessed as overusing analgesic drugs in the last two months were excluded from the study. All patients were evaluated at least 72 h after the end of the critical migraine phase and well before

the next attack, verified by the headache diary during a subsequent clinical examination. Ten healthy subjects, with no concomitant general, neurological or psychiatric disease, served as controls. They were 3 males and 7 females, aged 21–50.

### CO<sub>2</sub> laser recording

The recording procedure has been detailed in a previous report [4].

### Stimulation

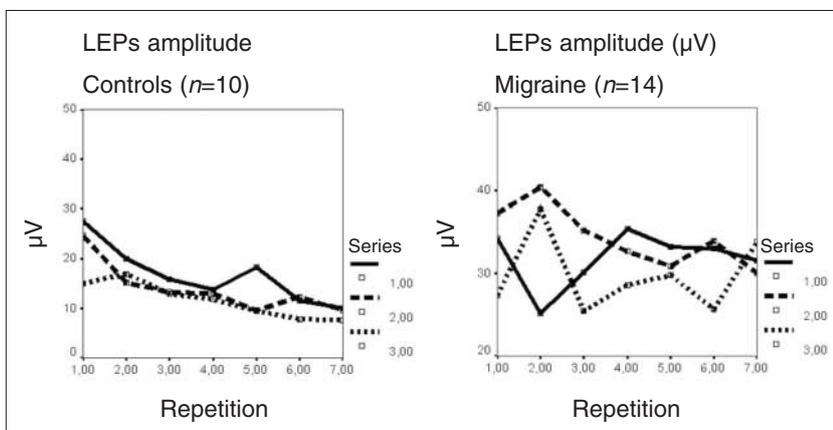
The right supraorbital zone was stimulated, according to the procedure previously described [4]. Three consecutive repetitions of 21 single responses were performed.

### LEP analysis

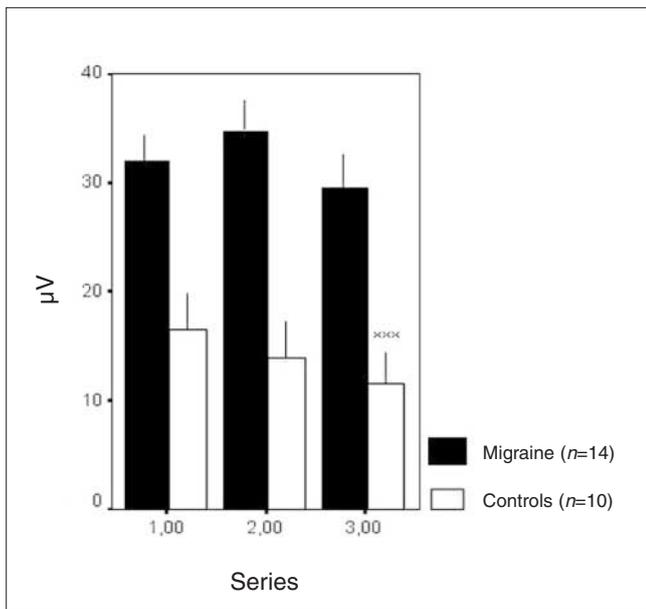
In the single repetitions, the single responses recorded to CZ derivation were detected and averaged off-line in groups of three consecutive responses. When the single response was not clear, a two-responses averaging was carried out. We obtained seven averaging for three repetitions in all cases. The N–P peak-to-peak amplitude was measured. The pain rating of the single stimuli (PR) was averaged across the repetitions.

### Statistical analysis

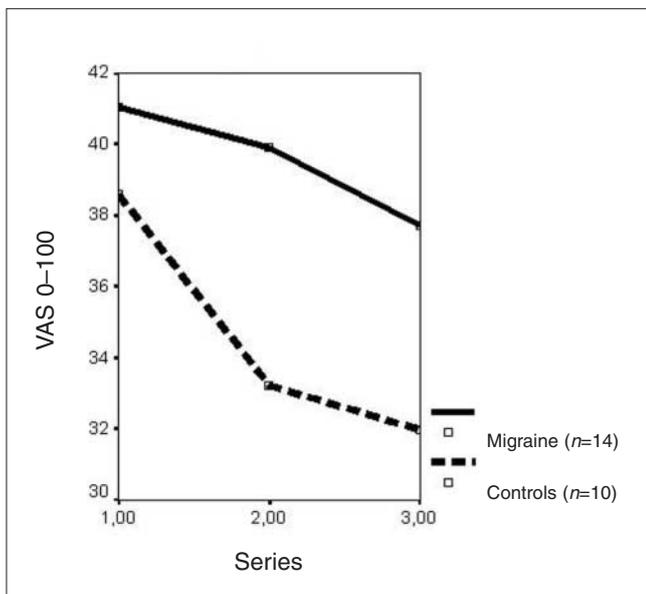
A two-way ANOVA with LEP amplitudes or pain rating as variables, and repetitions and series as factors was carried out in each group. In order to compare the two groups, a three-way ANOVA with LEP amplitudes or pain rating as variables, and cases, repetitions and series as factors was computed. Post-hoc, the Bonferroni test was also performed.



**Fig. 1** Mean values of LEP amplitudes ( $\mu\text{V}$ ) within the three series of stimulation and across the seven averaging of the 21 single responses in migraine patients and controls



**Fig. 2** Mean values and standard deviations of LEP amplitudes across the three series of stimulation. Results of Bonferroni test are shown: \*\*\* $p < 0.0001$  (first series vs. third series in control group)



**Fig. 3** Mean values and standard deviations of the pain rating of laser stimuli scored by a 0–100 VAS during the three series of stimulation in patients and controls

## Results

An increased LEP amplitude was found across the seven consecutive repetitions in the three series in migraine patients with respect to controls (ANOVA with LEP

amplitudes as variable and cases as factor:  $F=137.7$ ,  $p < 0.0001$ ). In the control group, the LEP amplitude significantly decreased across the seven repetitions and the three series (ANOVA with repetition as factor:  $F=11.77$ ,  $p < 0.0001$ ; ANOVA with series as factor:  $F=8.66$ ,  $p < 0.0001$ ) (Figs. 1 and 2). The Bonferroni test revealed that there was a progressive decline of LEP amplitude in the three repetitions, which was significant between the first and third repetition ( $p < 0.0001$ ) (Fig. 2). In the migraine group, no significant amplitude decline was observed across the seven repetitions ( $F=0.140$ ,  $p=0.991$ ) nor the three series of recordings ( $F=0.84$ ;  $p=0.43$ ) (Figs. 1 and 2). A slight and non-significant decline of pain rating was observed in migraine patients across the three repetitions ( $F=0.23$ ,  $p=0.79$ ). In the control group, the PR declined across the three repetitions ( $F=5.17$ ,  $p=0.049$ ). The Bonferroni test was not significant (Fig. 3).

## Discussion

The present results confirmed a pattern of deficient habituation under repetitive painful stimulation in migraine patients during the attack-free phase [2, 4], which was linked with deficient habituation of subjective pain rating, according to a previous report [4]. The novelty of this study was the detection of a habituation pattern of LEPs within a single series of stimulation: migraine patients exhibited higher LEP amplitudes than controls at the starting phase of stimulation, with a reduced decline across the consecutive repetitions. While control subjects showed quite a regular pattern of progressive LEP amplitude reduction, in migraine patients the LEP amplitude development was irregular, shifting from decrease to increase, with a final maintenance of the original amplitude and a loss of habituation across the three series of stimulation. This phenomenon corresponded to a loss of the reducing pattern regarding the pain rating. The present results could confirm an abnormal elaboration of painful stimuli at cortical level in migraine. The nociceptive cortex which subtends the LEP vertex complex is consistent with the operculo-insular regions and, in a prevalent way, the anterior cingulate cortex [6]. These cortical areas seem basally overactive in migraine, with a reduced pattern of habituation. The pattern of initial reduced amplitude followed by a reduced habituation as a compensatory phenomenon was observed for repetitive sensory stimulation [1, 5] as a sign of lower pre-activation level of sensory cortex. In migraine the nociceptive cortex shows a peculiar behaviour under repetitive stimulation, with a continuous pattern of higher activation, probably facilitating the onset and the persistence of headache.

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## Medication-overuse headache: pathophysiological insights

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**Abstract** Medication overuse headache (MOH) is a clinically important entity and it is now well documented that the regular use of acute symptomatic medication by people with migraine or tension-type headache increases the risk of aggravation of the primary headache. MOH is one of the most common causes of chronic migraine-like syndrome. Because of easy availability and low expense, the greatest problem appears to be associated with barbiturate-containing combination analgesics and over-the-counter caffeine-containing combination analgesics. Even though triptan overuse headache is not encountered with great frequency, all triptans should be considered potential inducers of MOH. There are several different theories regarding the aetiology of MOH, including: (i) central sensitisation from repetitive activation of nociceptive pathways; (ii) a direct effect of the medication on the capacity of

the brain to inhibit pain; (iii) a decrease in blood serotonin due to repetitive medication administration with alteration of serotonin receptors; (iv) cellular adaptation in the brain; and (v) changes in the periaqueductal grey matter. The principal approach to management of MOH is built around cessation of overused medication. Without discontinuation of the offending medication, improvement is almost impossible to attain. Thus, the best management advice is to raise awareness and strive for prevention. In this article, we analyse also the possible mechanisms that underlie sensitisation in MOH by comparing these mechanisms with those reported for other forms of drug addiction.

**Key words** Medication overuse headache • Migraine • Sensitization • Drug abuse • Obsessive-compulsive behaviour

### Introduction

Medication overuse headache (MOH) is a major clinical problem in most Western countries [1–5]. MOH has been recently introduced in the International Classification of

Headache Disorders [2]. The overuse of acute medications in patients who are suffering from headache represents a great challenge to headache management. MOH represents one of the most common iatrogenic disorders and possibly shares some pathogenetic mechanisms with other kinds of drug addiction. The recent development of acute

headache medications, especially the triptans, provided increased migraine relief. Nevertheless, the emergence of triptan overuse headache has also gained interest. Similarly, other symptomatic drugs for headache relief such as ergots, analgesics, opioids, morphinomimetics and barbiturates can cause MOH [1–5].

MOH is an interaction between a therapeutic agent used excessively and a susceptible patient. Awareness of MOH and familiarity with the diagnosis and treatment of this disorder are important to physicians who treat patients with headache. Features of migraine and tension-type headache often coexist in MOH. The diagnosis of MOH is clinically extremely important because patients rarely respond to prophylactic medications whilst overusing acute medications [6]. Furthermore, the understanding of the pathophysiological mechanisms underlying MOH may help to explore appropriate therapeutical strategies. The general term of MOH encompasses those headaches presenting more than 15 days per month [2].

Patients suffering from MOH represent a great number of patients referring to headache specialistic centres. Moreover, these patients have high frequencies of psychiatric comorbidity or psychologic distress in clinic-based studies [7]. The presence of psychologic distress contributes to poor quality of life in patients with MOH.

Overuse of various compounds frequently leads to a state of dependency. This kind of headache can be caused by the intake of combination analgesics, opioids, ergot alkaloids, aspirin, non-steroidal anti-inflammatory drugs, caffeine and triptans [1–6].

The most frequent cause for the transformation of a periodic headache into a chronic disabling headache is substance abuse. Substance abuse and drug dependency have multiple causes, and the aetiology resides with the compounds that are used to excess.

The problem may arise as a result of poor instructions from the physician, improper diagnosis with gradual escalation in amounts of drug consumed, or a reinforcement mechanism and a brain stimulation-reward effect. Frequent use ( $\geq 15$  times/month) of medication for the treatment of acute migraine attacks may cause MOH. The delay between first intake and daily headache is shortest for triptans (1–2 years), longer for ergots (3 years) and longest for analgesics (5 years) [1].

Analgesic and ergot alkaloid combinations with caffeine often lead to a relapse. However, patients overusing opioids have the highest relapse rate after withdrawal treatment.

Some studies have suggested that triptan overuse may increase migraine frequency to that of chronic migraine. Evidence suggests that this occurs sooner with triptan overuse than with ergotamine overuse.

Complete withdrawal from headache medication is the treatment of choice for MOH. Discontinuation of the

overused headache medication, however, results in the development of withdrawal headache, often associated with nausea, vomiting and sleep disturbances [1–6].

### **Drug-induced sensitisation and MOH**

Sensitisation is the enhanced response to a stimulus that occurs with repeated exposure to that stimulus. Psychostimulants are perhaps the best-studied drugs of abuse in terms of producing sensitisation. Behavioural sensitisation is the augmented motor-stimulant response that occurs with repeated, intermittent exposure to cocaine and amphetamine. Sensitisation is hypothesised to underlie the craving associated with drug abuse that may lead to relapse following a period of abstinence. In addition, cross-sensitisation occurs between drugs of abuse, suggesting that common mechanisms may underlie the development of sensitisation to drugs targeting different neurotransmitters [8, 9].

Certain features of MOH, namely, increased headache frequency, expansion of headache area and cutaneous allodynia, may imply sensitisation of central nociceptive neurons in the trigeminal pathway as well as in cells of the periaqueductal grey (PAG).

Repetitive activation of the trigeminal nerve can lead to a biologic and functional change in trigeminal nucleus caudalis neurons, characterised by a decrease in nociceptive threshold and receptive field expansion. Suppression of the endogenous pain control system can facilitate the process of central sensitisation [10]. A similar process might be also involved in the sensitisation induced by medication overuse in tension-type headache patients [8].

Sensitisation underlies the craving associated to drug abuse leading to relapse following a period of abstinence. In support of this hypothesis, sensitisation may last months to years following the cessation of drug exposure. Whether sensitisation may occur as a consequence of medication overuse in headache patients or it is caused by the repetitive occurrence of episodes of stressful events such as headache episodes is still unclear [11]. Nevertheless, behavioural correlates associated with MOH might partially resemble some of the more characteristic features of the behavioural sensitisation to psychostimulants. Among these features the most important are the requirement of repeated administrations during a certain period of time, the tendency to have a “craving” in the early phase of abstinence, and the occurrence of cross-sensitisation among different drugs used to treat headache. In addition, the tendency to reach a status in which the assumption of the drugs is induced by a “compulsive” and stereotypical behaviour rather than by real medical needs,

and the possibility to observe a relapse after relatively long periods of abstinence may resemble the characteristics of drug addiction [12].

The first step among the several biochemical changes required to induce synaptic plasticity and central sensitisation is an increased extracellular level of glutamate [8, 13]. A significant increase in glutamate levels has been detected in the cerebrospinal fluid of patients with chronic forms of headache [8].

Central sensitisation and storage of information at a cellular level also require changes at maintained transcriptional level. Several different intracellular signal transduction cascades converge on mitogen-activated protein kinase (MAPK), activation of which appears to be a master switch or gate for the regulation of central sensitisation via transcriptional regulation of key gene products. Thus, memory traces of painful events can be retained as a form of long-term increase in the efficacy of excitatory synaptic transmission [8, 10, 11].

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### **Are MOH patients sharing an obsessive-compulsive profile with other addictions?**

Psychiatric comorbidity, especially major depression, anxiety and panic disorders, has been found to be highly prevalent in patients with chronic headache and MOH [7, 14]. Comparing psychiatric comorbidity between migraineurs with and without chronic drug overuse a significantly higher prevalence of major depressive disorder, panic disorder and social phobia has been found in the patients with a history of chronic substance use.

Drug dependence disorders have been found to be associated with various comorbid psychiatric disorders including panic attacks, social phobia, specific phobia and obsessive-compulsive disorder (OCD) [15, 16].

Although neuropsychological and neuroimaging studies of OCD have implicated cortical areas, subcortical structures (i.e., the ventral and dorsal striatum) seem also to play a major role in the pathophysiology of the disorder. Accordingly, neuropsychological studies have

demonstrated that patients with OCD showed specific cognitive deficits on tasks of executive and visual memory function [8, 15, 16].

Patients with chronic headaches and MOH bear similarities to drug or substance abuse patients, for whom genetic liability loci have been implicated. Molecular genetic studies in this field are, however, still few and preliminary.

Shared neurobiological features characterise substance use disorders and other compulsive behaviours (alcoholism, pathological gambling, compulsive shopping, compulsive sexual behaviours, compulsive computer use). Thus, future clinical and genetic studies on the comorbidity between MOH patients, other forms of addiction and OCD are needed.

The common pathogenetic role of 5-HT in both MOH and OCD can establish an additional link between these two disorders. Moreover, it is worth noting that selective serotonin reuptake inhibitors (SSRI) are effective in the treatment of OCD but they may also represent a therapeutic option in MOH [8].

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### **Conclusions**

In recent years, advances in brain research have resulted in a striking strategic shift in studies designed to develop new, effective treatments for MOH as well as for related neuropsychiatric disorders. This involves a multidisciplinary approach with recursive interactions among respective disciplines with the ultimate goal of contributing to treatment development. New common perspectives for treatment of MOH, drug abuse and other related psychiatric disorders may arise from brain imaging and molecular and pharmacogenetic studies, showing a shared pathophysiological base among these disorders. Translational components of this research include the potential for integrating advances in brain imaging and molecular and pharmacogenetic assessments as they may potentially relate to neurodiagnostic assessment and treatment development.

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## Introduction to the new International Classification of Headache Disorders

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**Abstract** Based on the first edition of the classification (already validated), the ICHD-II is intended for not only the researcher and clinician but also the neurologist and general practitioner. All the headaches are classified into groups and subgroups to provide the level of diagnosis necessary for each user.

**Key words** Migraine • Nosography • Primary • Secondary

The main body of the new International Classification of Headache Disorders (ICHD-II) is composed of 4 parts (Table 1). *Part I*: The primary headaches (migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalalgias and other primary headaches); *Part II*: The secondary headaches (Chapters 5–12); *Part III*: The cranial neuralgias and central or primary facial pain and other headaches (Chapters 13 and 14) and Appendix.

The ICHD-II, like the first version, was rigidly structured as a descriptive classification for primary headache disorders, essentially constituting a definition of attacks, with scarce consideration for the evolution of the disease over time. Diagnostic criteria denominated “explicit”

were given to each recognised entity. The term “explicit” means unambiguous and precise, based almost exclusively on the clinical characteristics of each single attack, with the scope of leaving as little room as possible for interpretation of the terminology and the symptoms. The classification criterion adopted for secondary headaches is, instead, purely aetiological, even though the structure of the ICHD-II criteria has been standardised and the clinical characteristics of the various forms were added, where available.

Relying on the hierarchical classification already adopted in the first edition, and subsequently validated, the ICHD-II is intended for not only the researcher and clinician but also the neurologist and general practitioner.

**Table 1** Structure of the International Classification of Headache Disorders – II Edition

## Part one: The primary headaches

1. Migraine
2. Tension-type headache
3. Cluster headache and other trigeminal autonomic cephalalgias
4. Other primary headaches

## Part two: The secondary headaches

5. Headache attributed to head and/or neck trauma
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures
12. Headache attributed to psychiatric disorder

## Part three: Cranial neuralgias, central or primary facial pain and other headaches

13. Cranial neuralgias and central causes of facial pain
14. Other headache, cranial neuralgia, central or primary facial pain

## Appendix

All the headaches are classified into groups, which are then subdivided one, two or three times to provide the level of diagnosis necessary for each user.

The scarce attention given by the ICHD-II to the evolution of headaches could represent a limitation of the taxonomical system in clinical practice; nevertheless, this position was the result of an attentive and well-pondered choice, suggested by the lack of reliable information on the evolution of numerous forms of headaches, especially the primary types. Another aspect that has had a scarce impact on the classification is the one related to genetic

findings: despite the volume of data accumulated over the years, to the present day it has not been possible to identify monogenetic forms within the heterogenous group of phenotypes clinically described.

This was done with the purpose of stimulating the collection of evidence-based information that will eventually lead to the correct nosography. The ICHD-II Committee has created the Appendix, a section in which the headache forms that have not been clinically and diagnostically classified or diagnostic criteria that must be validated by research studies have been temporarily included.

**Suggested readings**

Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. *Cephalalgia* 24[Suppl 1]:9–160

Nappi G, Manzoni GC (2005) *Manuale delle Cefalee*. Masson, Milano

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## Application of ICHD 2nd edition criteria for primary headaches with the aid of a computerised, structured medical record for the specialist

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**Abstract** We tested the computerised, structured medical record by entering and analysing the consecutive clinical sheets of primary headaches in the episodic forms (200) and chronic headache (200) and the corresponding output diagnoses of patients attending our Headache Centre. A diagnosis of one of the primary headache forms was obtained in 67.9% of cases. A certain diagnosis of primary headache plus that of a probable form was obtained in 24.4% of cases (12.7% represented by chronic migraine (CM) or chronic tension-type headache (CTTH)+probable medication-overuse headache). Only probable forms were diagnosed in the remaining 7.3% (as single probable diagnosis in 5.8% of cases or multiple diagnoses of probable forms in the remaining ones). The percentage of certain diagnoses mainly in the chronic headache group (28.4%), and to a lesser extent tension-type headache (6.5%), were obtained in 34.9% of cases. A certain diagnosis of one chronic form plus that of a probable form was obtained in 50.8% of cases (26.9% represented by probable medication-overuse headache). Only probable forms

were diagnosed in 13.46% (as single probable diagnosis in 8.73% of cases or multiple diagnoses of probable forms in the remaining ones). In the other cases, the ICHD-II classification does not allow the diagnoses of CM, CTTH or probable forms and medication-overuse headache because the mandatory criteria for the diagnoses are too stringent and do not reflect modifications of the headache pattern in relation to its chronicity. These preliminary results underscore the usefulness of a computerised device based on the ICHD 2nd edition for diagnostic purposes in tertiary centres dedicated to headaches in clinical practice as well as its relevance for research. This computerised device may help to validate the new diagnostic criteria and to answer some emerging questions from the application of the new classification version, the relevance of which should be verified in clinical practice.

**Key words** ICHD 2nd edition • Classification criteria • Primary headaches • Computerised clinical sheet

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## Introduction

With the purpose of investigating the application of the 1988 IHS criteria in tertiary care centres dedicated to headache, in 1998 we set up an easy-to-use computerised structured record based only on the mandatory IHS requirements for the diagnosis of primary headaches, that is, migraine with and without aura, episodic and chronic tension-type headache (CTTH), and episodic and chronic cluster headache.

With the help of an expert (MP), a programme called "IHS Diagnostic Criteria for Primary Headache", was developed strictly based on the 1988 IHS operational diagnostic criteria [1], in Italian and international versions. This programme was set up using CA dBFast for Windows International (Computer Associates International, Inc., New York), an extended version of Dbase language for Windows. The programme was tested under Microsoft Windows OS 3.11, 95, 98 and NT 4.0. The use of Dbase archives (DBF) allows the direct transfer to other major software (i.e., Microsoft Excel), making statistical analysis easy and versatile. The programme operates in a stand-alone or LAN environment and is compatible with the main network systems under Microsoft Windows.

The computerised structured record encompassed the 1988 IHS criteria up to the second digit for all the above primary headaches. Before its use, the clinician should exclude any secondary headache by means of general and neurological examinations and, if necessary, proceed with laboratory and instrumental investigations.

Immediately after publication in 2004 of the International Classification of Headache Disorders (ICHD) 2nd edition [2], we implemented our computerised, structured medical record based exclusively on the proposed new classification system for primary headaches (2.0 version). In particular, our aim was to verify, with the aid of our computerised device, the application of the new ICHD-2 criteria in the clinical practice, especially considering some aspects, such as the introduction of probable forms, the definition of aura, and the introduction of chronic migraine (CM) as well as drug abuse. In the continuing search for potential applications of the new ICHD 2nd edition 2004, we updated the software that manages the relational database in which to save the personal data of the patient and the clinical data required for the diagnosis of primary headache, reaching a coverage of about 85%–90% of all headaches and almost the totality of primary headache diagnoses [3].

The new 3.0 version of "ICHD 2nd edition Diagnostic Criteria for Primary Headache", allows the diagnosis of all migraine subtypes to the second digit and of 1.2 *Migraine without aura* to the third digit (from 1.2.1 to 1.2.6). This level of diagnosis for migraine without aura was not present in the 2.0 version, as well as the capability to discriminate between 1.3, 1.4 and 1.5 migraine subtypes. The diagnosis of migraine complications was also completed, and now the level of migraine diagnosis from 1.5.1 to 1.5.6 is possible, whereas in the 2.0 ITA version, this was limited to 1.5.1 *Chronic migraine*.

**Fig. 1** First sheet of the computerised record in the latest version. It allows input of the mandatory variables for the diagnosis according to ICHD-II, such as number of attacks, duration of attacks, period of observation, pain characteristics (duration, location, intensity, quality), associated and accompanying symptoms

**Fig. 2** Second sheet of the computerised record in the latest version. It allows input of the variables relevant to aura, exclusion of a secondary headache, presence of pericranial tenderness (tension-type headache), cluster period duration and attack-free periods

**Fig. 3** Third sheet of the computerised record in the latest version. This third screen allows the user to return to screens 1 and 2, to access the output diagnosis, and also to save the data. There is also a button for access to an additional sheet dedicated to symptomatic and prophylactic treatment and for additional annotations

The module is now in beta 1 testing for the diagnostic category, 1.3 *Childhood periodic syndromes*, which are common precursors of migraine, and in time the software will also include this important migraine subtype, for which an additional screen will be dedicated.

As in the previous 2.0 version, the actual 3.0 version allows the diagnosis of tension-type headache to the third digit. The diagnoses of cluster headache allowed to the third digit were all covered as in version 2.0, but the other trigeminal autonomic cephalgias, 3.2, 3.3 and 3.4, which were lacking in the previous version, are now introduced to the second digit in the 3.0 version. The screens of the actual version of the computerised record are shown in Figures 1–3.

Moreover, our intention is to develop all subtypes included in the diagnostic group of headaches attributed to substances or their withdrawal, which is strictly bound to the diagnoses of CM and CTTH. At the moment, verification for the occurrence of drug abuse is entrusted exclusively to the clinician.

### Application of “IHS Diagnostic Criteria for Primary Headache” in the two versions, 1988 and 2004

#### First version (1988 IHS Classification)

We tested the computerised structured record based on 1988 IHS Criteria by entering and analysing data reported on the case sheets of 500 consecutive patients attending nine headache centres in Italy [4].

The rate of concordance between the diagnosis provided by the computerised structured record and that reported by clinicians on the case sheets was calculated, and reasons for any discrepancies between the two diagnoses were analysed. Concordance between the two diagnoses was found in 345 of 500 cases examined (69%). In the remaining 155 cases, diagnoses reached with the computerised structured record and the case sheets were impossible or discordant with respect to the diagnoses made by the clinician. In 144 of these cases

(28.8%), this was due to missing information or errors in the diagnosis recorded by the clinicians on the patients' case sheets.

In particular, the diagnosis could not be reached using the computerised structured record in 105 cases (20.6%), because of a lack of one or more pieces of data needed in formulating a correct diagnosis according to IHS operational criteria for one of the primary headache disorders. In the remaining 41 cases, some data were missing, but the data available were sufficient to reach a diagnosis according to IHS criteria. Moreover, the diagnoses reached using the computerised structured record were not in agreement with those made by the clinicians in another 39 cases (7.8%), due to an incorrect interpretation by the clinicians of the data reported on the patients' case sheets. In only 2.2% of cases ( $n=11$ ), misdiagnoses were due to programme errors that were promptly corrected. This study therefore suggests that incorrect application of IHS criteria for the diagnosis of primary headaches may occur in as many as one-third of patients attending headache Centres, and that use of a computerised structured record based exclusively on current IHS criteria may overcome this deficiency.

#### Second version (based on ICHD-2)

We tested the computerised structured record by entering and analysing different cases of primary headaches and the corresponding output diagnoses, with particular regard to the new entities introduced: diagnoses of probable migraine with and without aura, probable frequent and infrequent tension-type headache, CM and probable CM, and finally, probable tension-type headache.

First, we assessed the clinical chart and headache diaries of the first 200 consecutive patients who attended our Headache Centre in 2004, using the ICHD-II computerised system.

Diagnosis of one of the primary headache forms was obtained in 67.9% of cases. A certain diagnosis of primary headache plus that of a probable form was obtained in 24.4% of cases (12.7% represented by CM or CTTH+probable medication-overuse headache). Only probable forms were diagnosed in the remaining 7.3% (as single probable diagnoses in 5.8% of cases or multiple diagnoses of probable forms in the remaining ones).

Some cases, which were analysed using the 2.0 version of our record, prompted us to propose some modifications to the new diagnostic criteria for probable frequent and infrequent tension-type headache [5]. These proposals were published as a Letter to the Editor in one of the first issues of *Cephalalgia*, 2005 [6].

One example is the case with an output diagnosis of frequent episodic tension-type headache, which, based on the ICHD 2nd edition classification system, also fulfils criteria A and B for probable infrequent headache. This is because the diagnostic criterion A for probable infrequent episodic tension-type headache is misleading, stating: "Episodes fulfilling all but one of criteria A–D for 2.1 *Infrequent episodic tension-type headache*". To avoid this drawback, we propose to change criteria A and B for infrequent tension-type headache as follows: A. Headache episode occurring on <1 day per month on average (<12 days per year) for a period of >3 months and lasting from 30 minutes to 7 days. B. At least 10 episodes fulfilling criterion A. Criteria C–E remain unchanged. Consequently, we suggest the following definition for Criterion A of "2.4.1 *Probable infrequent episodic tension-type headache*": Episodes fulfilling criterion A and all but one of criteria B–D for 2.1 *Infrequent episodic tension-type headache*. Criteria C and D remain unchanged.

Another case is that for which we have 3 probable diagnoses: probable frequent headache, probable infrequent headache and probable migraine. Based on the modifications proposed above, one of the probable diagnoses can be excluded, and the differential diagnosis between two probable forms (i.e., probable frequent headache and probable migraine) remains. The clinical judgement in this case is pivotal.

#### 3.0 version (based on ICHD-II, implementation of 2.0 version)

After further implementation of our computerised record, we focused our attention on the first 200 consecutive patients with primary chronic headaches who attended our clinic in 2004. Certain diagnoses, mainly CM (28.4%), and to a lesser extent tension-type headache (6.5%), were obtained in 34.9% of cases. A certain diagnosis of a chronic form plus a probable form was obtained in 50.8% of cases (26.9% represented by probable medication-overuse headache). Only probable forms were diagnosed in 13.46% (as single probable diagnoses in 8.73% of cases or multiple diagnoses of probable forms in the remaining ones).

A small group of patients ( $n=7$ ) was identified who have 15 or more headaches per month, fulfilling the diagnostic criteria for both 1.5.1 *Chronic migraine* and 2.3 *Chronic tension-type headache*. This is considered in the classification in the comments to CTTH. The classification states, in fact, that it is possible to have the two diagnoses when two (and only two) of the four pain characteristics are present and headaches are associated with mild nausea. In these rare cases, other clinical evidence that is

not part of the explicit diagnostic criteria should be taken into account and the clinician should make the best possible choice of diagnosis based on this.

For 5 other patients, we obtained with our computerised record the diagnosis of both probable migraine and CM. These are the cases of patients who have migraine attacks for 15 days or more per month for more than 3 months but with a duration of attacks less than 4 hours, as stated in the diagnostic criteria for migraine without aura in patients >18 years of age. This was a minor imprecision of the software, which was immediately corrected on the basis of the comment to 1.6.1. *Probable migraine without aura*, where it is stated: “Do not code 1.6.1 *Probable migraine without aura* if the patient fulfils the criteria for 1.5.1 *Chronic migraine* or 1.5.2 *Status migrainosus*. In particular, we would like to point out that the diagnostic criterion A for CM states that headache should fulfil criteria C and D for 1.1 *Migraine without aura* on  $\geq 15$  days/month for >3 months, but not criterion B, which implies duration of headache attacks lasting 4–72 hours. In 11 cases the diagnosis of CM could not be obtained, despite the presence of migraine features and the occurrence for >15 days. This is because the observation period was <3 months in 1 case, criterion C for 1.1 was not fulfilled in 5 cases, or criterion D for 1.1 was not fulfilled in another five cases. A single interesting case with features of tension-type headache attacks had 6 probable diagnoses. The 2 diagnoses of probable infrequent and probable frequent headache were discarded according to modifications proposed by our group, whereas that of probable CTTH and probable medication-overuse headache remained, together with the additional diagnosis of probable migraine without aura. In 6 other cases we obtained the diagnosis of headache not classified. In one case it concerned a patient fulfilling all but one of the diagnostic criteria for “2.3 *Chronic tension-type headache*”. We would like, however, to mention in this regard that the diagnosis of probable CTTH only refers to a headache that fulfils all criteria of CTTH and is not attributed to another disorder, but is associated, within the last 2 months, with medication overuse, fulfilling criterion B for any subforms of 8.2 *Medication-*

*overuse headache*. Therefore, it can be attributed to patients fulfilling all but one criteria of CTTH when drug abuse does not occur. For 2 patients, the output diagnosis was headache not classifiable, because a chronic headache with migraine features and without medication abuse was present, which fulfilled all but one of criteria CD for “1.1 *Migraine without aura*” on  $\geq 15$  days/month for >3 months, given that in this as in the previous case, the term probable is exclusively limited to the presence of a medication overuse fulfilling criterion B for any of the subforms of “8.2 *Medication overuse headache*”. The situation is also more complicated in 3 additional cases and led to the diagnosis of headache non-classifiable when CTTH (1 patient) and CM (2 patients) fulfil all but one of criteria CE for tension-type headache occurring on  $\geq 15$  days/month on average for >3 months, or criteria CD for “1.1 *Migraine without aura*” on  $\geq 15$  days/month for >3 months, respectively, when medication overuse is present.

## Conclusions

The examples reported underscore the usefulness of a computerised device based on the ICHD 2nd edition for diagnostic purposes in tertiary centres dedicated to headaches in clinical practice as well as its relevance for research. This computerised device may help to validate the new diagnostic criteria and to answer some emerging questions, such as those presented above, arising from the application of the new classification version, the relevance of which should be verified in clinical practice.

This could surely help to clarify unsolved questions, and in this regard debate is needed among all the authors of the classification and among all those trying to apply the new diagnostic criteria, both in the clinical setting and in the research field. This should be the objective of the new group of IHS, which is dedicated to setting up a computerised system for headache diagnosis according to the ICHD 2nd edition classification, and our invitation to its members is to urgently commence work in this direction.

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## Development of a ICHD-II based computerised system for the general practitioner

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**Abstract** We present a computerised programme designed for use in the office of a general practitioner. The system provides an assisted diagnosis according to the ICHD-II criteria for the principal forms of primary headaches (migraine, tension-type headache, cluster headache) and highlights the red flags of a possible secondary headache. A relevant feature is that explanations for the selection of a particular diagnosis are given at the end of the process; furthermore, the characteristics of the patient's headache, which were previ-

ously inserted in the programme by the physician, are summarised, allowing critical evaluation of the suggested diagnosis. The software can also be used as a clinical file, in that it is possible to create for each patient a clinical chart in which to record the selected diagnosis, the recommended therapy and any eventual comments. Our programme aims for educational growth, promoting the learning of the basic ICHD-II criteria.

**Key words** Diagnosis • Software • International Headache Classification

### Introduction

In the clinical setting of a general practitioner (GP), migraine represents the most frequently observed neurological disorder [1], a point that reflects its distribution in the population. The prevalence of this primary headache ranges between 6% and 12% in males and between 15% and 18% in females, reaching a peak between the second and fourth decades of life, when productivity is greater, thus causing considerable social and economic costs [2]. In the absence of pathognomonic neuroimaging or laboratory tests, the recently revised diagnostic criteria (International Classification of Headache Disorders, 2nd edition, ICHD-II) [3] are the backbone of the diagnosis of migraine, which is based on an accurate medical history centred on the clinical characteristics of headache, and on the general

physical and neurological examinations; further verification is required when an underlying organic pathology is suspected of being responsible for the headache. The ICDH-II classification is structured in a ranked hierarchy: a code identifies each type of headache (the first digit corresponds to the first diagnostic level); a more detailed diagnosis entails the addition of other digits, corresponding to the more thorough diagnostic levels for a particular headache type, allowing its use not only in daily clinical practice but also in Headache Centres, or for research.

Unexpectedly, given the disability of the migraine attack (e.g., cancelled work and social activities, limitations in the care of the family, reduced work productivity), a high percentage of patients (30%–70% according to different studies) has never undergone a specialised medical visit [4]; among the principal causes given by the patients themselves is the belief in the inefficacy of therapy. In the

case of medical consultation, the professional figure who was first consulted by more than 40% of migraineurs was the GP [5]. The workload of GPs obliges them to optimise the length of the visit, thus making it often difficult to properly diagnose the headache, which *per se* requires that adequate time be dedicated to each patient. The consequence of a too quick approach to the migraine sufferer can prevent a precise diagnosis and limit the quality of the therapeutic choices.

Knowledge of the ICHD-II criteria for the diagnosis of headaches [3], and in particular of the more frequent primary headaches, becomes indispensable for a correct diagnostic approach, preliminary to the choice of the most appropriate therapy for that particular form of headache. However, maintaining medical competency at its best is very difficult in a time characterised by the exponential increase of knowledge in this field, even more so in a setting such as that of the GPs, who must meet the diverse needs of their patients in very different areas. For this reason, we developed a computerised programme designed for use in the office of a GP, which completely revisits a previous version: the system provides an assisted diagnosis according to ICHD-II criteria for the principal forms of primary headaches (migraine, tension-type headache, cluster headache) and highlights the red flags of a possible secondary headache. A relevant feature is that explanations for the selection of a particular diagnosis are given at the end of the process. Furthermore, the characteristics of the patient's headache, which were previously inserted in the programme by the physician, are summarised, allowing critical evaluation of the suggested diagnosis. Completion

of the diagnostic workup is simplified by a system of windows containing informative notes and explanations of the terminology used, which is indicated by an appropriate symbol; moving the pointer of the mouse over it opens the window with the comments and related notes. If the presenting clinical picture bears anomalies or is unusual, the programme advises the interviewer to request an in-depth visit by a specialist; the same advice, this time with the diagnosis, is provided if the characteristics of the headache are compatible with a rare form of primary headache (for example SUNCT syndrome).

The software can also be used as a clinical file, in that it is possible to create for each patient a clinical chart in which to record the selected diagnosis, the recommended therapy and any eventual comments; the clinical chart can be updated at each successive follow-up. Therefore, once the procedure has become familiar, our programme is also a valuable time-saving tool.

This programme accomplishes a twofold objective. Firstly, it provides the GP with support during the diagnostic evaluation, offering also a didactic content consisting of explanations and summary notes that appear along the steps of the programme and with the final diagnosis. Secondly – and this, together with the simplicity of the programme interface, represents the most interesting feature of this software – our programme is not a passive diagnostic instrument producing more or less “automatic” diagnostic labels, but instead constitutes aims for educational growth, promoting the learning of the basic ICHD-II criteria, and hence the critical attitude of the GP in his clinical approach to the headache patient.

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## Osmophobia in primary headaches

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**Abstract** This study evaluates osmophobia (defined as an unpleasant perception, during a headache attack, of odours that are non-aversive or even pleasurable outside the attacks) in connection with the diagnosis of primary headaches. We recruited 775 patients from our Headache Centre (566 females, 209 males; age  $38 \pm 12$  years), of whom 477 were migraineurs without aura (MO), 92 with aura (MA), 135 had episodic tension-type headache (ETTH), 44 episodic cluster headache (ECH), 2 chronic paroxysmal hemicrania (CPH) and 25 other primary headaches (OPHs: 12 primary stabbing headaches, 2 primary cough headaches, 3 primary exertional headaches, 2 primary headaches associated with sexual activity, 3 hypnic headaches, 2 primary thunderclap

headaches and 1 hemicrania continua). Among them, 43% with MO (205/477), 39% with MA (36/92), and 7% with CH (3/44) reported osmophobia during the attacks; none of the 135 ETTH and 25 OPH patients suffered this symptom. We conclude that osmophobia is a very specific marker to discriminate adequately between migraine (MO and MA) and ETTH; moreover, from this limited series it seems to be a good discriminant also for OPHs, and for CH patients not sharing neurovegetative symptoms with migraine. Therefore, osmophobia should be considered a good candidate as a new criterion for the diagnosis of migraine.

**Key words** Osmophobia • Migraine • Primary headaches • International Headache Classification

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### Introduction

In the new International Headache Society (IHS) classification [1], the alternative criteria for the diagnosis of migraine without aura that are reported in the appendix differ from the original criteria only in point D, which requires the presence of at least two of the following: nau-

sea, vomiting, photophobia, phonophobia and osmophobia. According to the Diagnostic and Therapeutic Guidelines of the Italian Society for the Study of Headaches [2], the presence of osmophobia is reported in the additional clinical information in favour of the diagnosis of headache; moreover, the Guidelines of the Canadian Headache Society [3] recommend in their criteria for the diagnosis of migraine the presence of osmo-

phobia, which is judged to be highly sensitive and specific for migraine.

Intolerance to smell is often reported by migraine patients; despite this, the relationship between osmophobia and headaches has not been investigated in depth. Only two studies have evaluated the presence of osmophobia in migraine attack. The first, prior to the formulation of the IHS criteria [4], demonstrated it in 40% of 50 migraineurs studied [5]; the second, in a more recent study in a larger patient population, revealed the presence of osmophobia in 25% of migraineurs [6]. In a recent epidemiologic study of a Latin American patient population, osmophobia in migraineurs was said to be "almost always" present in 47.7% of subjects [7]. No study has ever been conducted that considered this phenomenon in relation to the different forms of primary headache.

### Subjects and methods

We conducted a clinical study on a randomised sample of headache patients referred to our Headache Centre. The patients suffering from migraine were divided into those without (MO) and those with (MA) aura; others suffered from episodic tension-type headache (ETTH), cluster headache and other trigeminal autonomic cephalalgias (TACs), and other primary headaches (OPHs). The diagnosis was formulated on the basis of the diag-

nostic criteria of the 2004 IHS classification [1] following a history performed with a semi-structured questionnaire, general physical and neurological examinations, and, if needed, the exclusion of a secondary cause of headache by laboratory and/or diagnostic tests. Study exclusion criteria were concomitant migraine and ETTH, or other headaches, in the same subject; also excluded were patients with a diagnosis of probable primary headache.

A semi-structured questionnaire was administered to all patients to evaluate the eventual presence of osmophobia during a headache attack.

### Results

A total of 775 patients (566 females, 209 males; age  $38 \pm 12$  years) were recruited from our Headache Centre, of whom (Table 1) 477 had MO, 92 MA, 135 ETTH, 44 episodic cluster headache (ECH), 2 chronic paroxysmal hemicrania (CPH), 25 other primary headaches (OPHs: 12 primary stabbing headaches, 2 primary cough headaches, 3 primary exertional headaches, 2 primary headaches associated with sexual activity, 3 hypnic headaches, 2 primary thunderclap headaches and 1 hemicrania continua). Among them, 43% with MO (205/477), 39% with MA (36/92) and 7% with CH (3/44) reported osmophobia during the attacks; none among the 135 ETTH and 25 OPH patients suffered this symptom (Table 2).

**Table 1** Study population

Diagnosis	<i>n</i>	Age, years	F	M
Migraine without aura (MO)	477	$38 \pm 12$	379	98
Migraine with aura (MA)	92	$37 \pm 11$	21	92
Episodic tension-type headache (ETTH)	135	$37 \pm 12$	95	40
Episodic cluster headache (ECH)	44	$39 \pm 12$	7	37
Chronic paroxysmal hemicrania (CPH)	2	$72 \pm 3$	2	0
Primary stabbing headache	12	$38 \pm 18$	8	4
Primary cough headache	2	$50 \pm 28$	0	2
Primary exertional headache	3	$43 \pm 23$	1	2
Primary headache associated with sexual activity	2	$37 \pm 10$	1	1
Hypnic headache	3	$63 \pm 11$	0	3
Primary thunderclap headache	2	$38 \pm 11$	1	1
Hemicrania continua	1	40	1	0
Total	775	$38 \pm 12$	566	209

**Table 2** Patients who referred osmophobia (*n*) during an attack

Diagnosis	<i>n</i>	Total study population	%
MO+MA	241	569	42
ETTH	0	135	0
ECH+CPH	3	46	7
OPHs	0	25	0

## Discussion

The diagnosis of primary headache is fundamentally clinical, in that there is no specific diagnostic test or biological marker with pathognomonic value available at present. The negative results obtained between attacks in the general and neurological examinations is a constant in primary headaches, and together with the clinical history, allows the physician to reach a diagnosis in most of the cases. Different authors [8, 9] have demonstrated the validity of the semi-structured questionnaire, which is able to examine accurately the medical history of the patient, avoiding the subjective aspects of the enquiry. Furthermore, recently a self-administered questionnaire was evaluated for the diagnosis of migraine in primary care [10]. Since 1988, the IHS [4] has utilised a classification system that defines headaches on the basis of mainly anamnestic-clinical operative criteria; this classification was recently updated [1].

Osmophobia is often referred to during a migraine attack in association with phono- and photophobia. In the appendix of the second edition of the International Headache Society Classification [1], osmophobia has been proposed in the associated symptoms category of the criteria for the diagnosis of migraine. This symptom

has not been studied, however, in relation to the forms of primary headache.

In our study of 775 patients, 42% with migraine and 7% with ECH reported osmophobia during the attacks; none among the ETTH and the OPH patients suffered this symptom. Interestingly, among osmophobic ECH patients, 2 of 3 patients also reported nausea, phono- and photophobia during the attacks; osmophobia seems therefore to be present in the forms of ECH sharing neurovegetative aspects with migraine.

## Conclusions

Osmophobia was not referred to by the patients with ETTH and OPH headaches; thus it can be considered a peculiar symptom of migraine in respect to these forms of primary headaches. Moreover, from this limited series it seems to be a good discriminant also for OPH, and for ECH patients not sharing neurovegetative symptoms with migraine. On the basis of these data, osmophobia should be considered a good candidate as a new criterion for the diagnosis of migraine.

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## A validation study of an Italian version of the ID Migraine: preliminary results

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**Abstract** Migraine is a highly prevalent and disabling disease that is substantially undiagnosed in primary care. Recently, the ID Migraine, a self-administered questionnaire, was shown to be a valid and reliable screener for migraine in primary care in the USA. To validate an Italian version of the ID Migraine, we planned a multicentric study, evaluating at least 220 patients affected by various form of headache. The responses to the questionnaire were compared with the diagnosis of headache made by a headache specialist blind to the result of the questionnaire. Sensitivity, specificity, and positive and negative predictive values for migraine were calculated. The statistical analysis on 140 patients now examined showed a very good performance of the ID Migraine with high sensitivity: 0.94 (95% CI: 0.89–0.95), specificity: 0.70 (95% CI: 0.54–0.86) and positive predictive value: 0.89 (0.82–0.95). If confirmed, these results would establish ID Migraine as a valid screening instrument for migraine in Italian headache patients and warrant further investigation in primary care to assess the validity of this ID screener in Italian population.

**Key words** Migraine • ID migraine • Italian ID migraine • Migraine recognition • Headache centers • Primary care

## Introduction

Although migraine represents an important cause of temporary disability [1, 2], as shown by recent surveys, about 50% of persons with migraine, even those with disabling headache, have never consulted a physician for the problem [3]. Moreover, only one third of migraine sufferers are currently treated with a prescription drug [4]. The low rates of diagnosis and treatment have several causes, including low medical consultation specifically for headache. Improving recognition of migraine in primary care will increase the rate of successful treatment with effective migraine-specific therapies. Recently, Lipton et al. validated a very brief self-administered questionnaire, consisting of only 3 items, the ID Migraine, for screening of migraine headache in primary care practice (PCP) [5]. ID Migraine was found to be a very good tool for recognition of migraine sufferers, showing very high sensitivity, specificity and positive predictive value (PPV) for migraine headache in a primary care setting.

The aim of the present study was to validate an Italian version of ID Migraine, to be used for migraine screening in Italian headache patients.

## Subjects and methods

We planned a multicentric study involving several headache centres to evaluate at least 220 consecutive patients affected by various forms of headache. The size of the sample to be examined was determined taking into account the prevalence of migraine headaches.

Consecutive headache patients aged 18–65 years referring to the headache centres involved in the study and reporting at least two headaches in the last three months were eligible for the study; according to the inclusion criteria used by Lipton et al. [5], patients had also to indicate that they had experienced at least a headache that interfered with their lives. Each patient completed an Italian version of the ID Migraine (Fig. 1), previously translated by Pfizer, which also has the copyright of the original ID Migraine. Pfizer authorised the authors to use the Italian version of the ID questionnaire for screening of migraine in an Italian headache population.

Patients gave their informed consent to participate in the study, which was approved by the local ethics committee.

According to Lipton et al. [5], the response to each item was treated as a binary variable with a “no” assigned to responses of “never” or “rarely” and “yes” assigned to responses of “less than half the time” or “half the time or more.”

After completing the questionnaire, patients were evaluated by a board-qualified headache specialist blind to the result of the ID Migraine. He performed a complete clinical evaluation including medical history, physical examination, comprehensive neurologic history and examination (including additional diagnostic tests if clinically indicated), and made headache diagnosis according to the criteria of the new classification of the International Headache Society (IHS), which was considered the gold standard [6].

The responses to the items of the questionnaire were then compared with the diagnosis and the validity was assessed calculating sensitivity, specificity, positive (PPV) and negative (NPV) predictive values. Test-retest reliability was evaluated in an independent sample of 20 patients that repeated the questionnaire 2–5 days after, through Kappa coefficient for intraclass correlation.

## Results

We have now evaluated 140 patients (F/M: 98/42, mean age: 38±12.7) affected by various forms of headache, about 60% of the sample to be examined. Seventy per cent of them (98 patients; F/M: 71/27; mean age: 36.7±11.8) were affected by migraine and the remaining 30% (42 patients; F/M: 28/14; mean age: 36.7±11.8) by non-migraine headache. In this last group 67% had tensive, 10% cluster and 23% other headaches. Table 1 shows sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of positive responses to the ID items for the diagnosis of migraine.

Analysis of the single questions showed high values of sensitivity and PPVs for each item (>80%), disability reaching the highest score in sensitivity 0.98 (0.96–1.01); and photophobia the highest PPV: 0.89 (0.82–0.96). Specificity had generally lower scores; lower scores were observed also in NPV for all items

Questionario ID Migraine:		
Durante gli ultimi tre mesi ha avuto i seguenti disturbi contemporaneamente al mal di testa?		
1. Ha avuto nausea o conati di vomito?	sì	no
2. Le ha dato fastidio la luce (molto di più di quando non ha mal di testa)?	sì	no
3. Il mal di testa ha limitato, per almeno un giorno la sua capacità di lavorare, studiare o fare quello che deve?	sì	no

Fig. 1 Italian version of the ID Migraine