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ISTITUTO NAZIONALE NEUROLOGICO "CARLO BESTA"
Centro Regionale per la Diagnosi e Cura delle Cefalee e delle Algie Cranio Facciali

FOCUS ON HEADACHES AND FACIAL PAIN: RECENT ADVANCES IN MECHANISMS AND MANAGEMENT

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Facial pains that cannot be classified among the migraines are frequently observed in everyday clinical practice.

In addition to the stabbing pains associated with all neuralgias (trigeminal, glossopharyngeal, etc.), these often include even bilateral chronic pains with localised poussèes, such as atypical facial pains, post-herpetic facial neuralgias, the facial pains associated with multiple sclerosis or optical neuritis, and painful ophthalmoplegias.

At the beginning of 2004, after years of work involving the world's leading researchers, the International Headache Society (IHS) published the second edition of its "Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain", the most serious attempt yet to give some kind of order to the complexity of craniocephalic pains. Among the cranial neuralgias and other causes of central facial pain, it speaks of "persistent idiopathic facial pain", which is assimilated to the old term of "atypical facial neuralgia" and used to define "a persistent facial pain that does **not** have the characteristics of cranial neuralgias, and is **not** associated with objective signs or a demonstrable organic cause". If classic is the definition of "neuralgia", which is used to designate "any short-lasting paroxysmal pain occurring at irregular intervals, whose topography is strictly limited to the area of innervation of a sensitive nerve or one of its branches, without any demonstrable gross alterations in the anatomical integrity of the nerve itself" (obviously referring to the idiopathic form), the definition of "persistent idiopathic facial pain" is conspicuous for a lack of "positive" defining characteristics, being delineated principally in terms of what is absent.

Therefore, this nosographical classification is lacking (and therefore simplistic) when it comes to defining a patient suffering from craniofacial pain in everyday clinical practice, in which it becomes clear that, especially in the case of so-called "atypical neuralgias", what should be a definition is not much more than a catch-all expression encompassing very different pathogenetic and clinical manifestations.

This indicates the no longer acceptable confusion concerning the use of the term "atypical facial neuralgia" which, however, continues to induce anyone seeking enlightenment from any book on Neurology to learn mistaken clinical interpretations. The aim of this Seminar organised by the Carlo Besta National Neurological Institute is to provide an opportunity for discussion and the exchange of ideas with the objective of preparing new diagnostic and therapeutic recommendations that are essential when dealing with such a complex pathological phenomenon.

The Seminar will see the participation of internationally known experts and is intended to become a point of reference for all specialists in the field.

I would finally like to thank the ARCA Association, which has been close to me in all of the scientific initiatives I have tried to promote in the past and, once again, has offered its enthusiastic support for this meeting.

Gennaro Bussone

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KEY NOTE LECTURE

G. Bussone • V. Tullo

Reflections on the nosology of cranio-facial pain syndromes

Abstract Orofacial pain syndromes have traditionally been divided into two groups: the typical neuralgias and atypical facial pain. While typical neuralgias are well characterised, the term atypical facial pain (now persistent idiopathic facial pain) covers a variety of poorly defined head and face pains whose aetiological mechanisms are poorly understood. This paper examines the characteristics and nosography of these conditions, and suggests they should not be considered as *neuralgias* (section 13 of the 2004 IHS classification) but as *other primary headaches* (section 4).

Key words Cranial neuralgias • Typical neuralgias • Atypical facial pain • Persistent idiopathic facial pain

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Introduction

The classification of the various forms of facial pain seems simple but close examination reveals some complex issues. The problem is illustrated by standard neurology texts, which dedicate just a few lines to atypical facial pain (new IHS terminology: persistent idiopathic facial pain) but treat the typical neuralgias (new terminology: cranial neuralgias) much more fully. An atypical facial pain is one *that does not possess the characteristics of a typical neuralgia and is not associated with physical signs or demonstrable cause*, while a typical neuralgia is *a brief duration, paroxysmal pain confined to the distribution of one or more branches of a sensory nerve, in the absence of evident damage to the nerve*.

The inadequacy of these definitions is evident from clinical practice: patients suffering forms with very diverse clinical characteristics may all be diagnosed with atypical facial pain, so the category appears as a holdall for a miscellany of conditions, probably of varying pathogeneses, and certainly with no uniform set of clinical characteristics. This lack of precision is reflected in the paucity of epidemiological studies on these pain forms, and our consequent ignorance of their real prevalence; although the clinical experience of headache specialists is that they are not rare.

Atypical facial pain was first proposed as a distinct clinical entity in the 1920s. Neurosurgeons at the time noted that 10%–15% of patients with chronic facial pain did not have the brief paroxysmal attacks typical of trigeminal neuralgia, and did not benefit from trigeminal surgery. Such patients, mostly women, often suffered a deep dull, sometimes burning, pain in the facial region spreading to the orbit, temple, ear, jaw, shoulder and arm (districts outside the distribution of the trigeminal nerve). The pain was continuous, in about 2/3 of cases, unilateral, might last hours, days or even longer, and there was no trigger zone. Nevertheless, the literature is replete with cases of highly variable characteristics: forms that begin episodic and become chronic; forms

continuous at outset; forms characterised by mild continuous pain punctuated by more severe attacks; forms characterised by long spontaneous remissions; and so on. In about half these cases autonomic manifestations, such as reddened swollen face, conjunctival injection, lacrimation, photophobia, anisocoria, sweating, salivation, rhinorrhea and nausea accompany the pain.

One pathogenetic proposal was that these conditions were vascular in nature and this idea was supported by some reports of favourable responses to vasoconstrictor drugs. However, vasoconstrictor efficacy was not confirmed in more extensive studies, and the vascular hypothesis has been abandoned. The autonomic manifestations that commonly accompany these conditions suggest autonomic nervous system involvement; however neither trigeminal root sectioning nor cervical sympathectomy are effective in controlling the pain, and this idea was also abandoned.

Psychogenic causes have been postulated since the earliest descriptions, in view of the fact that patients often have neurotic, hysteric, depressive or other altered personalities. Furthermore, antidepressive drugs, particularly tricyclic antidepressives, are often effective. Nevertheless many patients – who often respond well to amitriptyline – do not have personality disturbances, so these conditions cannot always be psychogenic.

Thus, the pathogenesis of atypical facial pain is uncertain, and probably multi-faceted; it is also important to consider that some atypical facial conditions may have an organic cause – inflammatory, neoplastic or vascular – and it is important to exclude this possibility in a patient, particularly when the pain has the characteristics of an atypical neuralgia.

Historically, therefore, there has been considerable confusion regarding the use of the terms atypical facial pain and neuralgia, and it is fair to say that this confusion still persists. The diagnostic criteria and headache classification published by the International Headache Society (IHS) [1] in 1988 proved highly successful in classifying the primary headaches and was the first serious attempt to impose nosographic order on the cranio-facial pain forms. However, analysis of the IHS characteristics criteria reveals that, while the typical neuralgias are well defined in terms of pain characteristics, topography (branches of cranial nerves) and specific therapeutic indications, atypical facial pain is conspicuous for a lack of "positive" defining characteristics, being delineated principally in terms of what is absent. Thus, the pain must *not* have the characteristics of the cranial neuralgias, and is *not* associated with physical signs or a demonstrable organic cause (Table 1). But what characteristics should atypical facial pain have? The 1988 classification states that the pain should be *present daily and persist for most or all the day*, and may be *poorly localised*. The comment section is not really helpful either: *the pain may be initiated by operation or injury to face, teeth or gums but persist without any demonstrable local cause*. There was no attempt to delineate these conditions from the pathophysiological point of view.

These comments should not be taken as overly severe criticisms of the 1998 classification, which attempts to be scientific and rigorous in the absence of more ample data. The fact is that atypical facial pains are highly variable. They include facial and dental pains, may accompany primary headaches, can also manifest without concomitant headache, or occur as predominant phenomena accompanying a "background" headache. In general practice, atypical facial pains tend to be given little consideration and are lumped together with the primary headaches, while for dentists, pain phenomena involving the teeth and surrounding areas, in the absence of an identifiable lesion, are a common occurrence. These conditions are generally treated by orofacial surgeons or at centres specialising in odontostomatology and temporomandibular disturbances. Thus, the "atypical" facial pains are much more frequent than "typical" forms, indicating that the term "atypical" is completely inappropriate.

In 2004 the revised version of the IHS headache classification was published [2] but was disappointing for its con-

Table 1 International Headache Society, 1988 [1]

12.8 Facial pain not fulfilling criteria in groups 11 and 12
Previously used terms: atypical facial pain, atypical odontalgia

Description: Persistent facial pain that does not have the characteristics of the cranial neuralgias classified above and is not associated with physical signs or a demonstrable organic cause.

Diagnostic criteria:

A. Is present daily and persists for most or all of the day.
B. Is confined at onset to a limited area on one side of the face. May spread to the upper or lower jaws or a wider area of the face or neck. Is deep and poorly localised.
C. Is not associated with sensory loss or other physical signs.
D. Laboratory investigations including X-ray of face and jaws do not demonstrate relevant abnormality.

Comment: Pain may be initiated by operation or injury to face, teeth or gums but persist without any demonstrable local cause.

servative approach to atypical facial pains. There was at least a name change – they are now called *persistent idiopathic facial pain* – but they are still defined mainly negatively with the pain poorly localised and the condition not associated with sensory loss, other physical signs or imagining abnormalities (Table 2). Adoption of the term *idiopathic* is significant, as it suggests something unknown, and in this respect is more informative than *atypical*; it includes diagnoses such as *atypical facial pain*, *atypical dental pain*, *muscular disorders of mastication* and *traumatic neuralgia*. However, these categories serve only to emphasise our limited understanding of facial pain syndromes.

We can make a fundamental distinction between neuralgic pain and myofascial pain. Neuralgic pain conditions can be continuous or intermittent. Intermittent pain is that of the traditional "typical" neuralgias, characterised as brief and intense, like an electric shock or similar. A recent suggestion is that these pain episodes are due to nerve compression, typically as a result of neuro-vascular conflict, but also tumour, exostosis, oedema, etc. Continuous neuralgic pain, which may fluctuate in intensity and is typically described as a burning or dull pain, is more difficult to explain. Three mechanisms are likely to be involved in its genesis: peripheral nerve compression, nerve regeneration with formation of neuroma and sympathetic hyperactivity following peripheral nervous system damage.

Myofascial pain, which may affect any muscle, is distinguished by the presence of triggers points whose stimulation may cause referred or local pain. If the trigger point is "active", it is painful on palpation and often gives rise to reproducible referred pain, sometimes of autonomic type, in distant structures. If the trigger is "silent", palpation produces local pain but not referred pain. Several mechanisms have been proposed to explain the propagation of the pain, but convincing explanations of initial triggering mechanism are lacking.

As noted, the new IHS classification has not changed the diagnostic criteria for persistent facial pain, however a comment has been added that a facial pain located in the area of the ear or temple may be associated with undiagnosed lung cancer which causes referred pain as a result of vagal involvement. This comment introduces the idea of symptomatic, as opposed to idiopathic, persistent facial pain, but once again its clinical features are undefined.

It is evident therefore that the atypical facial pains constitute a considerable medical problem, however, that have been marginalised and neglected. The classification that considered the cranial neuralgias as typical pain and everything else as atypical not only contributed to this marginalisation but was a disaster from the therapeutic point of view as it suggested that also atypical syndromes may be treated surgically.

At our Headache Centre in Milan at least 3% of patients with migraine and tension-type headache refer to associated dental or facial pain, and 1.2% of headache patients are diagnosed as having atypical facial pain (now persistent facial pain). Although these patients describe an intense and often debilitating pain (with associated compromise in quality of life), they do not appear to the physician to be suffering acutely and always refer to the pain as poorly localised. Most (70%) of these patients are women. Atypical odontalgia and burning mouth syndrome are probably localised variants of atypical facial pain.

Depression and anxiety are often associated with these facial pain syndromes. Conventional analgesics including opioids are usually ineffective and surgical procedures often aggravate the pain. Tricyclic antidepressives and psychotherapy seem the most reliable therapeutic approaches to these conditions but are by no means always effective.

To diagnose persistent idiopathic facial pain, any organic cause must first be excluded by magnetic resonance imaging and other appropriate examinations. These consid-

Table 2 International Headache Society, 2004 [2]

13.18.4 Persistent idiopathic facial pain
Previously used term: atypical facial pain

Description: Persistent facial pain that does not have the characteristics of the cranial neuralgias described above and is not attributed to another disorder.

Diagnostic criteria:

A. Pain in the face, present daily and persisting for all or most of the day, fulfilling criteria B and C.
B. Pain is confined at onset to a limited area on one side of the face and is deep and poorly localised.
C. Pain is not associated with sensory loss or other physical signs.
D. Investigations including X-ray of face and jaws do not demonstrate any relevant abnormality.

Note: Pain at onset is commonly in the nasolabial fold or side of the chin, and may spread to the upper or lower jaw or a wider area of the face and neck.

Comments: Pain may be initiated by surgery or injury to the face, teeth or gums but persists without any demonstrable local cause. Facial pain around the ear or temple may precede the detection of an ipsilateral lung carcinoma causing referred pain by invasion of the vagus nerve. The term atypical odontalgia has been applied to a continuous pain in the teeth or in a tooth socket after extraction in the absence of any identifiable dental cause.

erations suggest that facial or dental pain conditions without apparent cause are accessory, occasionally isolated, symptoms of primary headaches.

Conclusions

My suggestion is to recognise the "atypical" facial pain conditions as a species of primary headache, so as to eradicate the idea that the surgical interventions used to treat the "typical" neuralgias might usefully be applied to the "atypical" conditions, which respond best to therapies used to treat primary headaches. To achieve this it is important to change the classification of these headache forms, removing *persistent idiopathic facial pain* from section 13 (neuralgias) and inserting it in section 4 (other primary headaches). An attempt should be made to render diagnostic criteria more "positive", although this will require more intensive study of these hitherto neglected conditions.

Atypical facial pains should be considered as a type of primary headache because of the continuous deep and burning nature of the pain, which may sometimes also be pulsatile, and because the location does not correspond with that of a nerve distribution. Whether such pains should be treated, in a given patient, with anti-migraine medication, psychopharmaceuticals, or both will depend on the neurologist's judgement and the patient's history; an experienced clinical eye will best ascertain the extent to which psychogenic factors contribute to the symptomatology.

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G.C. Manzoni • P. Torelli

Epidemiology of typical and atypical craniofacial neuralgias

Abstract Trigeminal neuralgia (TN) has a prevalence of 0.1–0.2 per thousand and an incidence ranging from about 4–5/100 000/year up to 20/100 000/year after age 60. The female-to-male ratio is about 3:2. A review of several case series shows that pain is more predominant on the right side, but the difference is not statistically significant. TN is significantly associated with arterial hypertension, Charcot-Marie-Tooth neuropathy, glossopharyngeal neuralgia (GN) and multiple sclerosis. GN has an incidence of 0.7/100 000/year and epidemiological studies have shown it to be less severe than previously thought. Post-herpetic neuralgia has a comparable incidence to idiopathic TN. The epidemiology of the central causes of facial pain is still unclear, but it is known that persistent idiopathic facial pain is a widespread, not easily manageable problem.

Key words Epidemiology • Cranial neuralgias • Trigeminal neuralgia • Glossopharyngeal neuralgia • Post-herpetic neuralgia

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Introduction

Few reports have been published so far on the epidemiological aspects of the various forms of typical and atypical craniofacial neuralgias. For most of the 19 forms listed at the two-digit diagnostic level of Chapter 13 (cranial neuralgias and central causes of facial pain) of the International Classification of Headache Disorders – second edition (ICHD-II) [1], there are no data about their actual spread. In many cases, the lack of epidemiological studies is the result of methodological constraints due to classification difficulties and also the rarity of these conditions.

The few epidemiological data currently available are about trigeminal neuralgia (TN) and glossopharyngeal neuralgia (GN). Indirect evidence also exist for trigeminal post-herpetic neuralgia (PHN) and for certain forms of centrally caused facial pain.

Trigeminal neuralgia

The only indication about the *prevalence* of TN comes from a study by Penman [2], who in 1969 reported rates of 107.5/1 000 000 in men and 200.2/1 000 000 in women. TN is therefore a rare disease (about 1 case in every 10 with cluster headache).

More data are available on the *incidence* of TN. Penman himself [2] reported rates of 4.7/100 000/year in men and 7.1/100 000/year in women. In their accurate review of Rochester health records in the four decades between 1945 and 1984, Katusic et al. [3] found 75 TN cases (55 women and 20 men), with an incidence of 4.3/100 000/year (3.4/100 000/year for men and 5.9/100 000/year for women). Rozen [4] reported an overall incidence of 2–5/100 000/year for men and women. The few data currently available on TN incidence seem to be quite consistent; if they are applied to the Italian population, it can be reasonably assumed that in this country there are about 9000 people with TN and about 3000 new cases every year.

TN incidence progressively increases with increasing age: from 17.5/100 000/ between 60 and 69 years of age up to 25.6/100 000/year after 70 [3].

The *female-to-male ratio* was 1.74:1 in the Katusic et al. study [3] and 3:2 in another study by Ashkenazi and Levin [5].

A *family basis* for TN was reported as early as 1940 by Harris [6], who among 1433 TN cases found 30 (2%) who had a relative with similar facial pain. Recently, Smyth et al. [7] reported on a family with 4 TN cases in 3 generations, suggesting a dominant autosomic form of transmission. Terrence and Fromm [8] reported a familial inheritance in 4%–6% of cases. In the 75 TN patients investigated in Rochester, Katusic et al. [3] found 4 cases with a family history of the disease (5.3%); however, only in 3 cases (4%) was the affected person a first-degree relative. Selby [9] was right in warning that "*caution has to be exercised in accepting patients' statements that their parents and grandparents had tic douloureux (TN), since it is rare and other kinds of facial pain are common*".

Looking at the different case series, it appears that the *side* of the head affected by pain is more often the right one (43 of the 75 cases reported by Katusic et al. [3]), even though the differences are not statistically significant. Pain on both sides of the head is rare: 1 out of 75 cases in the Katusic et al. study [3] and 5.5% of the cases reported by Harris [6], who however found bilateral pain in 6 (20%) of his 30 patients with a positive family history.

TN appears to be significantly associated with certain disorders. Nineteen of the 75 patients studied by Katusic et al. [3] had *arterial hypertension*. Using age- and sex-specific prevalence rates for hypertension in Rochester resulted in an expected number of 9.7. The odds ratio for arterial hypertension was 1.96 (95% confidence interval, 1.2–3.1).

The literature reports 15 cases of TN associated with *Charcot-Marie-Tooth neuropathy* [7].

A possible comorbidity of TN with *glossopharyngeal neuralgia* has also been reported. Rushton et al. [10] found as many as 25 TN cases in 217 patients with GN; only in 9 cases did the two forms of neuralgia occur simultaneously.

However, the pathological association that has most captured the interest of researchers is that between TN and *multiple sclerosis* (MS). Three women among the 75 TN patients (4%) of Katusic et al. [3] had a history of MS prior to TN diagnosis compared with an expected number in all patients of 0.15. The estimated relative risk was 20.0 (95% confidence interval, 4.1–58.6). In a clinical population of 1882 MS patients, Hooge and Redekop [11] found 35 TN cases (1.9%). In 5 of them, TN was the first symptom of MS and preceded later manifestations of the disease by 1–11 years. Considering the 35 patients together, however, TN occurred on average 11.8 years after MS onset. In 14% of cases, TN was bilateral. MS onset was later (mean age, 39.2 years) in cases with TN than in those without TN (mean age, 29.9 years). The onset of MS-associated TN (mean age, 51 years) was not different from that of idiopathic TN, except in the 5 cases in which TN was the first symptom of MS (mean age at onset of TN, 38.2 years). Recently, Solaro et al. [12] found 36 TN cases in 1672 MS patients (2.2%).

Glossopharyngeal neuralgia

GN is a rare condition: according to Rushton et al. [10], its incidence is 1/70–1/100 that of TN. While confirming its rarity, more recent evidence indicates less marked differences over TN incidence. In their review of the Rochester health records for the four decades between 1945 and 1984, Katusic et al. [13] found 12 cases (7 men and 5 women) of GN. Mean age at onset was 64 years. Incidence was 0.7/100 000/year (0.9 and 0.5 in men and in women, respectively). Pain location was on the left side in 7 cases out of 12, on the right side in 2 and on both sides in 3. In spite of the small size of their patient sample, Katusic et al. [13] were able to reach interesting epidemiological conclusions by comparing their case series with the larger case series of Rushton et al. [10]. In particular, they found that GN is not generally a severe condition, because: (a) mild attacks are not uncommon; (b) the average annual recurrence rate for a second episode is low (3.6%); (c) two-thirds of the cases had only 1 episode; and (d) only one-fourth of the cases had to have surgery for relief of symptoms. Like TN, GN too may be significantly associated with MS. In a population of 8000 MS patients followed up over 20 years at the University of Miami in the US, Minagar and Sheremata [14] found 4 patients (0.5%, 2 men and 2 women) with GN.

Post-herpetic neuralgia

According to Bogduk [15], considering all possible sites of infection, acute herpes zoster (shingles) has an incidence of 131/100 000/year. Elderly and immunosuppressed patients are at greatest risk of developing the disease. Ragazzino et al. [16] reported that the trigeminal nerve was involved in 13% of cases: in 80% of these cases, it was the first branch that was affected.

About 10% of cases with acute herpes zoster eventually develop PHN, with marked age-related differences: while this is an unusual complication before 30 years of age, it becomes more frequent after 60, with an over 60% rate. Generally, PHN has a prolonged clinical course and in about 50% of cases is still present after 1 year.

A study by Watson [17] may give an idea of the actual frequency of trigeminal PHN. He found that in about 25% of all cases the trigeminal nerve is involved. By successive extrapolations from his data, it can be reasonably assumed that the incidence of trigeminal PHN is 3.3/100 000/year (20/100 000/year after age 60).

Central causes of facial pain

Unfortunately, there are very few epidemiological data on the central causes of facial pain, coded at 13.18 of ICHD-II [1], which includes 5 subtypes. Virtually nothing is known about the frequency of *anaesthesia dolorosa* (code 13.18.1) and of *burning mouth syndrome* (code 13.18.5).

As for *central post-stroke pain* (code 13.18.2), if one considers that about 1.5% of stroke cases that develop central pain post- [18] and that in about 33%–52% of these cases pain is located in the face, it can be estimated that central post-stroke facial pain occurs in about 1 in every 100–200 stroke cases.

A total of 43% of MS patients complain of significant pain, mostly of suspected central origin [12, 19]. In a multicentre cross-sectional study on the prevalence of pain in MS, Solaro et al. [12] found dysaesthetic pain in 18.1% cases, but unfortunately they did not indicate the pain site, so it is not possible to know how many had *facial pain attributed to MS* (13.18.3).

The spread of the clinical entity that ICHD-II [1] describes as *persistent idiopathic facial pain* (code 13.18.4), but that was previously known as atypical facial pain or chronic facial pain, is still largely unclear. According to Madland and Feinmann [20], orofacial pain is a common problem affecting at least 10% of the adult population and 50% of the elderly population, and its inadequate recognition and management present an enormous problem to the health service. Atypical odontalgia, which can be considered as a subtype of persistent idiopathic facial pain, occurs in 3%–6% of patients who undergo endodontic treatment [21]. There is a female preponderance with a concentration of cases of women in their mid-40s. Except for children (no reports have been found in the literature), all ages can be affected.

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Typical facial neuralgias

Abstract Neuralgia denotes a sharp, shooting, lancinating pain that is momentary but characteristically recurs. It may be precipitated by touch to a sensitive area ("trigger zone"), or may occur spontaneously. Cranial neuralgias are commonly distinct in two groups: typical neuralgias and atypical facial pain. Unlike headache syndromes, which are mediated centrally, neuralgias are more characteristic of peripheral nerve localisation. Neuralgias may follow nerve trauma, herpes zoster infections or may arise spontaneously. The management of this group of painful conditions is complicated by the area of the body involved and the interaction of organic and psychological factors.

Key words Neuralgia • Pain • Typical

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Introduction

Typical facial neuralgias cause facial and intra-oral pain ranging from mild burning sensations to incapacitating lightning bolts of excruciating pain. The cranial nerves can be involved in mediating either neurogenic or nociceptive pain that is perceived as headache. Neurogenic pain arises when the axons or cell bodies are affected by intrinsic or extrinsic disorders and is manifest clinically as neuralgia.

The International Headache Society (IHS) classification considers all these painful syndromes in chapter 13 [1]. Trigeminal, glossopharyngeal, nervus intermedius, superior laryngeal and occipital neuralgia are well characterised entities, whilst atypical facial pain is usually referred to unclassifiable pain syndromes in the facial region and includes an ill understood group of conditions.

The main difference between the two forms, typical and atypical, is based on the pain quality. The former is a stabbing, lancinating, brief shock-like sensation, strictly unilateral and limited to the distribution of the cranial nerve affected. The pain is precipitated by trivial stimuli (trigger factors) and there is no pain between attacks. The latter is a continuous, drawing, burning, pressing or throbbing facial pain that typically does not follow anatomical boundaries, often with bilateral localisation [2].

Trigeminal neuralgia

Trigeminal neuralgia (TN), probably the best known of these painful conditions, was described as early as the first century A.D. in the writings of Aretaeus. An 18th-century French surgeon, Nicolaus Andre coined the condition "Tic Douloureux", which means "painful spasm". Traditionally, TN is described as "a painful unilateral affliction of the face, characterised by brief electric shock-like (lancinating) pains limited to the distribution of one or more division of the trigeminal nerve. The electric shock-like pain generally

is on one side of the face and is spasmodic, coming in short bursts lasting a few seconds to less than two minutes. Several attacks can follow each other within minutes. Eating, shaving, washing, applying makeup, brushing the teeth and talking can be triggers, but may also occur spontaneously. The pain is abrupt in onset and termination and may remit for varying period." The attack's pain is limited strictly to some part of the distribution of the trigeminal nerve. It usually starts in the second or in the third division, less than 5% in the first division. The pain never crosses to the opposite side but it may occur bilaterally, approximately in 3%–5%. Among cranial neuralgias, TN is the most common with an incidence of about 5/100 000 of the general population. In the majority of cases it occurs after the age of 50, and both sexes are equally affected [3, 4].

Several syndromes are closely related to TN, but have specific unique features as well. These include the so-called "trigeminal autonomic cephalalgias" (TACs), a group of syndromes that may have some clinical hallmarks of trigeminal-distribution pain with autonomic symptoms [5–7]. The group includes: cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection, tearing, sweating and rhinorrhoea (SUNCT).

As far as the aetiology is concerned, it is still controversial if all the TNs must be considered idiopathic or symptomatic [8, 9]. Typical TN may be observed as a symptom of neoplasms, artero-venous malformations, inflammatory diseases or vascular-nerve conflicts in the root entry zone (REZ) of the trigeminal nerve [10]. However, it is possible to find this disease in otherwise asymptomatic patients, especially over age 50 [11]. Although the aetiology of TN is still unknown, current thinking is that there is a peripheral disturbance or damage with cerebral brainstem disinhibition of the trigeminal apparatus. This condition results in a paroxysmal discharge and reverberation of pain impulses when a trigger point is elicited [12]. Up to now, no medical test exists that clearly diagnoses all cases of TN. TN diagnosis should not be difficult, especially in cases of classic TN where the symptoms are clear and distinct, though CT scan or magnetic resonance imaging (MRI) are mandatory. In some cases, high definition MRI angiography of the trigeminal nerve and the brain stem can identify where the nerve is compressed by a vein or artery [13]. Initial treatment of TN is usually medication, with carbamazepine being the first drug of choice. Likewise, other antiepileptic drugs as oxcarbazepine, lamotrigine and gabapentin, often used alone or in combination [14]. They are effective in controlling trigeminal neuralgic pain in the majority of patients, at least in the initial stages. For unknown reasons however, medical treatment either is not effective from the beginning or fails after a few years. Surgery then becomes the only available therapeutic option.

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia (GN), is described as a deep stabbing pain in one side of the throat. GN, much less common than TN, is characterised by paroxysm of unilateral pain with sudden onset radiating from the oropharynx, the base of the tongue, tonsillar fossa or pharynx to the ear or vice versa. The pain usually last from 8 to 50 s but occasional attacks may continue for a few minutes and longer-lasting attacks have been reported. The attacks may present in clusters that last from weeks to months. The patient may have 5–15 attacks per hour, up to 300–400 attacks per day. Often the attack is triggered by swallowing, chewing, talking, coughing and turning the head. GN is occasionally accompanied by bradycardia, hypotension or syncope. The annual incidence rate is about 0.7/100 000 per year, suggesting that it is a rare disease. There is no significant difference between men (more affected) and women [15]. The vast majority of patients with GN are thought to have an artery compressing the nerve as it exits from the medulla and travels through the subarachnoid space to the jugular foramen. GN is a milder disease than TN, as indicated by the number of episodes, treatment and characterisation of pain; the pain is more variable than that seen in TN but usually responds initially to carbamazepine. Pain is equally divided between the two sides; bilaterality is not uncommon, more frequent than in TN. This syndrome can be seen in patients with multiple sclerosis, but it is rare [16].

Nervus intermedius neuralgia

Nervus intermedius neuralgia (NIN), sometimes known as geniculate neuralgia, is an extremely uncommon pain syndrome in which the patient reports severe paroxysmal of stabbing and lancinating pain in the distribution of the nervus intermedius, which is the somatic sensory branch of cranial nerve VII. The pain is in every way similar to that of tic douloureux except for its location centred directly deep in the ear, in the auditory canal. Aetiology is referred to a cross compression of the nerve at its central-peripheral myelin junction, a few millimetres from the lateral pons. The pain can be triggered by non-noxious stimulation of the ear canal or can follow swallowing or talking. The syndrome is always unilateral. Lacrimation, salivation, bitter taste, tinnitus and vertigo are sometimes reported during the pain attacks. Association with herpes zoster is not uncommon. The medical management of NIN is identical to that of TN. When medications do not control the pain, a surgical procedure is warranted [17, 18].

Superior laryngeal neuralgia

Vegal and superior laryngeal neuralgia (SLN), the two somatic sensory branches of the vagus nerve, the auricular branch and the superior laryngeal nerve, can also be the site of a pain syndrome that resembles that of TN. SLN is a rare disorder characterised by paroxysms of shock-like pain in the side of the thyroid cartilage, pyriform sinus, angle of the jaw and, rarely, in the ear. The trigger zone is usually in the larynx and attacks are precipitated by talking, swallowing, yawning, coughing or turning the head The patients are usually middle-aged, healthy men. Lancinating paroxysms lasting seconds to minutes may also be triggered by straining the voice and occasionally may radiate to the posterior auricolar region, the shoulder, upper thorax or the palate. The pain usually lasts minutes or hours and varies markedly in intensity and may show remissions [19]. The pharmacological treatment of SLN is identical to that of TN. Surgical decompression of the upper fibres of the vagal nerve is warranted when medication does not control the pain.

Occipital neuralgia

Occipital neuralgia (ON) is characterised by pain in the suboccipital region and in the back of the head. Known causes of ON include trauma to the greater or lesser occipital nerves, compression of these nerves or the upper cervical roots by arthritic changes in the spine and tumours involving the 2nd and 3rd cervical dorsal roots [20]. The region of the pain clearly establishes the diagnosis, but the difficult task is to determine whether the nerve lesion is primary or secondary. A large number of patients have muscle tension headaches in the same distribution, but few of these patients have a true neuralgic pain with continuous aching and throbbing pain on which shock-like jabs can be superimposed. The pain is not triggered, but pressure over the occipital nerves can lead to an exacerbation. If the pains resemble those of TN, a trial of anticonvulsants might be worthwhile; if they resemble those of atypical facial pain, a tricyclic antidepressant can be tried [21]. Local nerve blocks can help to establish the diagnosis and sometimes provide even longer relief than the duration of the agent used. Neurosurgeons have advocated sectioning of the 2nd and 3rd cervical roots or the greater and lesser occipital nerves [22].

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Atypical facial pain: clinical considerations and differential diagnosis

Abstract Atypical facial pain (ATFP), recently defined as persistent idiopathic facial pain by the revision of the Classification of the International Headache Society (IHS), is a poorly understood condition, which still lacks clear diagnostic criteria and proper treatment. The pain is described as "persistent facial pain that does not have the characteristics of cranial neuralgias and is not attributable to another disorder". In general, however, according to the IHS criteria, a diagnosis of ATFP is possible when the pain in the face is present daily and persists for most or all of the day. The pain is confined at onset to a limited area on one side of the face, often in the nasolabial fold or side of the chin and may spread to the upper or lower jaw or a wider area of the face of neck and is deep and poorly localised. It is not associated with sensory loss or other physical signs. Laboratory investigations including X-ray of face and jaws do not demonstrate relevant abnormality. Pain may be initiated by operation or injury to face, teeth or gums but persists without any demonstrable local cause. But, the definition and the diagnostic criteria are over-simplified when we face the reality of the clinical practice. Many different disorders may be included in this diagnostic category, making differential diagnosis very complex. Diagnosis of ATFP is therefore, usually, a process of elimination. A targeted history and an accurate examination are crucial to correctly classify this facial pain.

Key words Atypical facial pain • Persistent idiopathic facial pain

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Chronic orofacial pain is a common and debilitating problem affecting at least 10% of the adult population and 50% of the elderly population [1]. It is a poorly understood condition that represents a challenge for clinicians in terms of diagnosis and treatment. This term refers to many different disorders, such as temporomandibular joint disorders, headaches, neuralgias, atypical facial pain (ATFP), pain of mucosal origin and dental pains. Patients suffering from orofacial pain may, therefore, seek and receive treatment from different practitioners, making this problem multidisciplinary. In 1999, Woda and Pionchon [2] proposed a unified concept of chronic idiopathic orofacial pain, including in this group ATFP, atypical odontalgia, masticatory pain, temporomandibular joint disorders and oral dysaesthesia. They stated that these conditions share a common clinical picture: they are more common in women, the pain does not follow a nervous pathway and is present for months, it returns periodically in the same form over several months or years, it has no major paroxysmal character, it is present through all or part of the day, it is absent during sleep and psychological factors are often present. Harris and Feinmann [3] suggested that the four syndromes of chronic idiopathic facial pain (ATFP, atypical odontalgia, temporomandibular joint disorders and oral dysaesthesia) often coexist or occur sequentially. Maier and Hoffmeister [4] included sympathetic dystrophy in the diagnosis of ATFP.

One of the disorders included in the group of chronic orofacial pain is ATFP. The term "atypical" was first used in 1924 by Frazier and Russell [5] and applied to patients with facial pain that failed to respond to neurosurgical treatment. In the past years many clinicians have tried to describe ATFP in different ways, with the only result being confusion and lack of clarity. The aetiology of ATFP is so controversial that some early authors refused even to accept that the condition existed [6].

In general, patients with this condition complain of a steady, generally unilateral and not well localised pain. The quality of the pain is usually described as deep, constant, aching, pulling or crushing. There are not paroxysms of short duration; the pain is usually present all day and every day. Although patients complain of excruciating pain, they do not usually appear to be in severe pain. ATFP is not triggered by any of the precipitating factors typical of neuralgias. Most of the patients with ATFP complain of other symptoms, including headache, neck and backache, dermatitis or pruritis, irritable bowel and dysfunctional uterine bleeding [1].

ATFP still lacks proper diagnostic criteria. The International Headache Society, in its revised classification in 2004, included ATFP as a "previously used term" under the classification heading "persistent idiopathic facial pain" (code 13.18.4) [7]. The society described this as 'persistent facial pain that does not have the characteristics of cranial neuralgias and is not attributable to another disorder'. According to these criteria, a diagnosis of ATFP is possible when the pain in the face is present daily and persists for most or all of the day. The pain is confined at onset to a limited area on one side of the face, often in the nasolabial fold or side of the chin and may spread to the upper or lower jaw or a wider area of the face of neck and is deep and poorly localised. It is not associated with sensory loss or other physical signs. Laboratory investigations including X-ray of face and jaws do not demonstrate relevant abnormality (but it does not mention specifically which types of investigations or radiographs should be used). Pain may be initiated by operation or injury to face, teeth or gums but persists without any demonstrable local cause. The pain around the ear or forehead may precede the diagnosis of an ipsilateral pulmonary neoplasm that causes a referring pain because of a vagus nerve invasion.

The society also described atypical odontalgia as a continuous pain in the teeth or tooth sockets in the absence of an identifiable cause, and also laid down criteria for a diagnosis of burning mouth.

The International Headache Society proposed these criteria but there is still uncertainty and no greater clarity. In the old classification of 1988 [8], the IHS described ATFP (code 12.8) as a persistent pain that does not have the characteristics of cranial neuralgias and is not associated with physical signs or a demonstrable organic cause. The diagnostic criteria were the same as the new one.

The aetiology of ATFP is still unknown. Some risk factors have been suggested as aetiologic factors, however any one can be considered as the causal. The role of female hormones has been implicated, as ATFP is much more common in women than in men and because of the physiologic and therapeutic modification of oestrogen levels in patients with these pain conditions. Osteoporosis, which appears with menopause, and neuralgia-inducing cavitational osteonecrosis have been linked to ATFP. The presence of psychosocial factors is also a common feature, but it is not known whether these are causal or whether the pain induces the psychosocial problem. In some cases, infection of the sinuses or teeth, or minor nerve trauma can also be considered as risk factors. However, none of the above factors can be considered as the sole aetiologic factor. Different neuropathic mechanisms may be at work: nociceptor sensitisation, phenotypic changes and ectopic activity from the nociceptors, central sensitisation possibly maintained by ongoing activity from initially damaged peripheral tissues, sympathetic abnormal activity, alteration of segmental inhibitory control, and hyper- or hypoactivity of descending controls [9].

ATFP must be distinguished from typical facial pains, primary headaches and dental pains. Table 1 summarises the characteristics of the most common disorders that have to be differentiated from ATFP. However, other rare conditions need to be considered when confronted by facial pain. In particular, trigeminal neuralgia is characterised by severe, quick bursts of pain in one or more branches of the trigeminal nerve. The bursts last only an instant and they recur irregularly during the day. The pain is described as excruciating and it is often triggered by facial movement, change of temperature or touching the face at a specific point (trigger point). Intensity is severe. It affects generally older people, with only a slight predominance in women. Sometimes patients with trigeminal neuralgia can have additional symptoms of ATFP [10]. The treatment consists, in general, of anticonvulsants.

Temporomandibular joint (TMJ) syndrome is characterised by focal tenderness of one or both TMJs and aggravation of pain by chewing, talking and lateral jaw movements. The quality or pain can be similar to that of ATFP; pain can be dull or stabbing. Intensity is moderate. The treatment consists of NSAIDs and surgery.

A relevant but not often considered condition is carotidynia. It is a chronic pain syndrome characterised by pulsating pain that arises from the carotid artery and radiates up the neck to include pain in the ipsilateral face, ears, jaws and teeth. Diagnosis is made by palpation of the carotid artery, which may elicit or increase the pain.

ATFP is usually without a specific cause. However, sometimes injury of branch of the trigeminal nerve due to facial trauma or basal skull fracture can produce the disorder. Imaging studies are normal but, on rare occasions, ATFP could be the presenting symptom of lung cancer. In

Table 1 Differential diagnosis of facial pain

Facial pain	Location	Quality	Intensity	Duration	Aggravating factors	Other characteristics
Trigeminal neuralgia	Second and third division of trigeminal nerve, unilateral	Lancinating, stabbing, burning, electric shock-like	Severe	Seconds	Touching or washing the face, eating, chewing, smiling, talking, blowing nose, yawning, brushing the teeth, shaving	–
Post-herpetic neuralgia	Usually opthalmic or maxillary branch of fifth nerve, unilateral	Aching, burning, jabs	Severe	Constant	Contact, movement	–
Atypical facial pain	One side of the face, nasolabial fold or side, chin, jaw, neck; poorly localized	Deep, aching, pulling, crushing	Moderate to severe	Constant	–	–
Temporomandibular joint syndrome	Jaw, mandible, preauricolar region	Dull, stabbing	Moderate	Minutes to hours	Palpation of the jaw joint or the muscles of mastication, mastication, prolonged talking	Incomplete jaw opening, clicking on lateral movements
Tolosa-Hunt syndrome	Mainly retro-orbital, unilateral	Aching	Severe	Constant	–	Ophtalmoplegias, sensory loss over forehead, ptosis, pupil usually spared
Raeder paratrigeminal syndrome	Fronto-temporal and maxilla, unilateral	Deep, lancinating	Severe	Constant	–	Ptosis, miosis
Carotidynia	Face, ear, jaws, teeth, upper neck, unilateral	Throbbing	Moderate	Constant	Compression of common carotid	–
Cluster headache	Orbital, suborbital, and/or temporal, unilateral	Variable	Severe	Minutes to three hours	Alcohol, stress, heat, cold, bright light	Autonomic symptoms
Tension-type headache	Frontotemporal and/or parietal, bilateral	Pressing, tightening	Mild to moderate	Minutes to days	–	–
Migraine	Frontotemporal, orbital, usually unilateral	Pulsating, throbbing	Moderate to severe	Hours	Physical activity	Aura in migraine with aura
Pulpitis	Teeth, other parts of the face, not well localized	Throbbing	Slight to severe	Minutes to hours	Mechanical, foods, cold, heat, suit	–
Orofacial tumours	Variable	Variable (atypical)	Severe	Slight to severe	Jaw movement	Frequently neurological signs, WBC abnormalities

this case, the facial pain is almost always unilateral, and is most commonly localised to the ear, the jaws and the temporal region. The pain is frequently described as severe and aching, and may be continuous or intermittent. Aggravation and expansion of the pain, digital clubbing, increased erythrocyte sedimentation rate and hypertrophic osteopathy may contribute to the diagnosis. Referred pain, due to invasion or compression of the vagus nerve, as well as paraneoplastic syndrome secondary to the production of circulating humoral factors by the malignant tumour cells, is implicated in the pathophysiology of facial pain associated with non-metastatic lung cancer. Radiotherapy and tumour resection with vagotomy are very effective in aborting the facial pain. Thus, lung cancer should be included in the dif-

ferential diagnosis of facial pain that is atypical and/or refractory to treatment [11].

Treatment of ATFP can be difficult and unsatisfactory. It consists mainly in patients' education and in pharmacotherapy with tricyclic antidepressants. Some anticonvulsants (phenytoin, carbamazepine, gabapentin, lamotrigine) can be less effective. Analgesics and surgical procedures such as microvascular decompression are not effective. Other pain relief strategies include hot and cold compresses, acupuncture, biofeedback and dental splint.

Diagnosing ATFP is not easy. It is not unusual that patients with ATFP undergo numerous dental procedures, see many doctors and undergo many medical tests before being successfully diagnosed and treated. A diagnosis of ATFP is usually a process of elimination. When a patient complains of constant facial pain restricted to one side of the face, the physician must first rule out any other conditions. A targeted history and an accurate examination are crucial to correctly classify this facial pain [12].

Despite the recent classification of the IHS [7], older terminology still seems to be widely used. A recent survey conducted in UK [13] aimed to compare views of UK specialists in dentistry and medicine who deal with chronic facial pain on their use of the term ATFP, how they reach this diagnosis or their alternative preferred equivalent diagnosis and what treatment they recommend. The study showed that 89% of practitioners from the various specialties in the UK who treat facial pain still use the term ATFP. To make the diagnosis of ATFP, 48% of specialists excluded other kinds of pain, 22% said they used certain criteria and 17% said that they used both methods. Although most of these specialists mentioned that they used the diagnosis-by-exclusion approach, it is not clear how they did this. Despite the fact that strong psychological factors may be present, there was no tendency among the various specialists to refer these patients to psychiatrists or for psychotherapy.

Management of ATFP requires a specific knowledge of the diagnostic criteria. This is extremely important in the process of differential diagnosis and in the choice of the most accurate and effective therapeutic treatment strategy. Facial pain has appreciable impact on the population. Many problems remain unsolved because causal mechanisms are unclear. Compounding the problem, the nosology is complicated by liberal uses of the terms "atypical" and "idiopathic", which are vague and overlapping.

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Controversies in optic neuritis pain diagnosis

Abstract Optic neuritis (ON) refers to any inflammatory disorder of the optic nerve. In clinical practice ON is mainly diagnosed by ophthalmologists and less frequently by neurologists. ON diagnostic criteria are included in different classification systems both in neurologic and ophthalmologic fields. Diagnosis of ON is still very unsatisfactory. Indeed diagnostic criteria are not uniform and therefore the diagnosis is still mainly formulated according to the clinical experience only. A consensus on practice guidelines for ON diagnosis might be useful. Ocular pain is a milestone in ON diagnosis, but it is too often mistreated by both the patient and the clinician. The International Headache Society (IHS) Classification of Headache Disorders provides in its 1988 and 2004 versions the diagnostic criteria for ON. These criteria are not spread and followed by the large majority of neurologists, but they are mainly applied by the experts in headache disorders. On the other hand, ON is a disorder widely encountered by neurologists and ophthalmologists. The latest IHS version defines the criteria of the pain features more precisely, but it is still unsatisfactory. In a future revision, the pain should be further detailed. Further studies aimed at validation of the diagnostic criteria of ON are strongly needed.

Key words Optic neuritis • Pain • Diagnostic criteria

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Optic neuritis (ON) refers to any inflammatory disorder of the optic nerve, but it usually denotes an acute or subacute disease of the optic nerve attributed to inflammation associated with demyelination. ON is the most common acute optic neuropathy in the 15–50 age group. Women are more often affected than men. ON has an incidence of 1–5 per 100 000 per year. The incidence is highest in Caucasians, in countries at high latitudes and in spring. In the absence of signs or symptoms of multiple sclerosis (MS) or other systemic disease, ON may be referred to as idiopathic or monosymptomatic [1–3].

The typical clinical profile of ON (Table 1) is represented by an acute unilateral visual dysfunction with ocular pain aggravated by eye movements [1]. Ophthalmological evaluation shows visual loss with decreased visual acuity, impaired colour vision and contrast sensitivity, a visual field defect, and a relative afferent pupillary defect. Most visual field defects involve the central field and may be of any type: central scotomas, altitudinal defects, monocular hemianopic defects. One third of patients have optic disc swelling. Optic pallor develops after 4–6 weeks. Among participants in the Optic Neuritis Treatment Trial (ONTT), ocular or periorbital pain was reported in 92% of the cases, 87% of which noted worsening of the pain by eye movement.

Visual acuity often worsens over several days, with a nadir typically within 1–7 days, followed by spontaneous improvement over several weeks [4]. Most of the improvement develops usually within 4–6 weeks, although there may be a slow continuous improvement for up to one year.

It is crucial for the neurologist to distinguish visual loss due to optic nerve dysfunction from other causes (Table 2).

Table 1 Typical features of ON

Age at onset between 18 and 45 years
Prevalence in women
Retro-orbital pain particularly with eye movement
Monolateral or bilateral visual loss
Abnormal colour vision and sensitivity to contrast
Central or cieco-central scotoma
Afferent papillary defect in the eye of abnormal function
Optic disc normal (retrobulbar ON) or oedematous (papillitis)
Progression of visual loss in 1–2 weeks
Visual evoked potential slow and diminished in amplitude in response to direct stimulus
In many patients with isolated ON, MRI shows cerebral white matter lesions (CIS=Clinically Isolated Syndrome)

Table 2 Differential diagnosis of ON

Multiple sclerosis
Neuroretinitis
Devic's syndrome
Behçet's syndrome
Post-infectious
Post-immunisation
Acute disseminated encephalomyelitis
Systemic inflammatory disease: SLE, sarcoidosis, autoimmune
Infections: Lymes, syphilis, tuberculosis, viral
Ischaemic optic neuropathy: anterior ischaemic optic neuropathy, posterior ischaemic optic neuropathy, giant cell arteritis, diabetic papillopathy
Leber's hereditary optic neuropathy
Compressive: primary tumours, metastases, tubercolomas, thyroid ophthalmopathy, arterial aneurysms
Toxic: methanol, ethambutol, chloroquine, streptomycin, chlorpropamide, chloramphenicol
Nutritional: Vitamin B12 deficiency, tobacco-alcohol amblyopia, Cuban and Tanzanian epidemic optic neuropathies
Ocular: posterior scleritis, maculopathies and retinopathies

This can usually be accomplished based on specific features of the history and bedside examination. Once it has been established that a patient has some form of optic neuropathy, several clinical features are helpful in determining the aetiology. The most important is the time course. Other factors include the presence or absence of pain, pattern of visual loss and funduscopic appearance. The presence or absence of pain does not seem to correlate with the severity of visual loss or the ultimate visual prognosis.

In most cases by using this information it is possible to differentiate among common forms of optic neuropathy: i.e., papilloedema, ischaemic optic neuropathy, ON, compressive lesion, toxic/nutritional deficiencies and hereditary forms.

The management of patients with central visual loss requires an accurate neuro-ophthalmological examination in order to distinguish signs and symptoms of optic nerve dysfunction from those due to other ocular structure damage.

Atypical features for ON include a progressive course, absence of pain, optic atrophy at presentation, lack of significant visual improvement and age over 40 years. For nonarteritic anterior ischaemic optic neuropathy (NAION), the atypical features include progressive course, optic atrophy at presentation, absence of vasculopathic risk and previous transient visual loss. Atypical clinical features of optic neuropathy require further specific laboratory, neurophysiological and imaging tests for a correct and early diagnosis [5].

Pain in and around the eye is a common complaint [6, 7]. Most ophthalmologic conditions producing eye pain are associated with obvious ocular symptoms and signs (e.g., redness, cloudy cornea, proptosis, diplopia and visual loss), and the neurologist should recognise these ocular presentations. Patients with a possible intraocular or intraorbital aetiology for pain should be referred to an ophthalmologist.

Lee reviews ocular and orbital disorders that produce eye pain without visible pathology of the eye, pain syndromes with predominantly ophthalmologic findings and ophthalmologic presentations of selected headache syndromes [6]. Acute optic neuropathy due to an intracranial lesion may masquerade as ON or NAION. Alternative causes of ON should be rigorously considered if a patient does not follow the typical clinical course or has a normal magnetic resonance imaging of the brain.

In order to identify the origin of pain in ON it should be remembered that the optical nerve itself is pain insensible. The pain accompanying ON is believed to result from irritation of the meninges surrounding the optic nerve. The sensory innervation of the eye and periocular region results from the first (ophthalmic) and second (maxillary) division of the trigeminal nerve. Recurrent branches of the trigeminal nerve also supply the intracranial dura, venous sinuses and cerebral vessels. Therefore headache of nonocular cause is often referred to the eye and orbit, and the pain of primary ocular origin often radiates to other parts of the head and the face.

The mechanism of the periocular pain on eye movement in ON is believed to arise from the close attachments of the superior and medial recti muscles to the optic sheath at the orbital apex. Contraction of the eye muscles with eye movement pulls on the inflamed optic nerve sheath and causes pain [8]. Papillitis is less frequently painful as the anterior nerve sheath or scleral opening is not subjected to the local traction of extraocular muscles and the larger subarachnoid and subdural space just behind the eyeball may impede extension of inflammation from the nerve to the sheath. Although distension of the meninges by a swollen optic nerve has been related to ON pain, the absence of pain in papilloedema, which is also characterised by sheath enlargement, should exclude meningeal distension as a primary pain source.

In ON the incidence of pain may be variably dependent on the localisation of the inflammatory process [9]. It is complained of more frequently when ON involves the orbital segment of the optic nerve and it is more often absent when the orbital segment is not involved. The pain associated with ON seems not to have specific characteristics. Several studies indicate that while there is an overlap in the incidence and features of pain in NAION and ON, there are no specific characteristics that can be utilised for differential diagnosis [10].

In clinical practice the management of acute ON is accomplished by neurologists and ophthalmologists, who markedly vary in their treatment approach. A consensus on practice guidelines on this issue might be useful [11, 12]. ON is mainly diagnosed by ophthalmologists and less frequently by neurologists.

Diagnostic criteria for ON are reported in different classifications in the neurological or in the ophthalmologic fields. The Classification of the International Headache Society (IHS) has considered the problem of the Optic Neuritis Diagnostic Criteria since the 1988 version [13], code 12.1.2.1, and in the Revised Version in 2004 [14], code 13.13. In the former version the criteria were: A. Pain is felt behind the affected eye; B. Central vision becomes impaired due to a central or paracentral scotoma; C. No extrinsic lesion can be demonstrated. In the actual version the diagnostic criteria are: A. Dull pain behind one or both eyes, worsened by eye movement and fulfilling criteria C and D; B. Visual impairment due to a central or paracentral scotoma; C. Onset of pain and onset of visual impairment separated by <4 weeks; D. Pain resolves within 4 weeks; E. A compressive lesion as been ruled out.

Nevertheless diagnostic criteria are not uniform and therefore the diagnosis of ON is still mainly formulated according to clinical experience only. Indeed, ophthalmologists in clinical practice often refer patients to neurologists with suspected ON based on visual impairment only.

The IHS Diagnostic Criteria of ON are based on a scarce amount of evidence [14]; moreover no studies have addressed their validation. Recently a study [15] was conducted to evaluate the clinical features of ON patients. The study design included a retrospective evaluation followed by a prospective analysis, with the aims first to verify the application of the ON IHS criteria in clinical practice and second to check whether the pain and its characteristics are used as qualifying aspects of the diagnosis of ON. The results of the study are reported in Table 3. The authors compare these results with the diagnostic criteria reported both in the 1988 and in the 2004 versions of the IHS Classification. According to the new IHS Criteria the percentage of patients fulfilling the ON diagnostic criteria is reduced compared to that obtained with the previous IHS Criteria (1988). The new diagnostic criteria of the ON describe the features of the pain more in detail, but their accuracy makes problematic the use in the clinical practice. The authors suggest that the pain is a milestone in ON diagnosis, but it is too often mistreated by both the patient and the clinician.

In conclusion, the IHS Diagnostic Criteria of ON are an important support to clinicians, but they do not fully satisfy the clinical characteristics for a correct diagnosis. In the future, firstly a revised version of the ON diagnostic criteria should contain further details for the pain, secondly the specificity and sensitivity of the diagnostic criteria should be revised based on validation studies, and thirdly the IHS Criteria should be diffused and followed by the large majority of clinicians, and not only by experts in headache disorders.

Table 3 Pain characteristics in patients with optic neuritis

	Retrospective study, %	Prospective study, %
Presence of retro-orbital pain	71	68
Spontaneous	21	0
Provoked by eye movements	37	41
Spontaneous and worsened by eye movements	42	59

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L. La Mantia • A. Erbetta • G. Bussone

Painful ophthalmoplegia: an unresolved clinical problem

Abstract Painful ophthalmoplegia (PO) is an important presenting problem to ophthalmologists and neurologists. The etiological differential diagnosis is extensive, including different syndromes and causes (vascular, neoplastic, infectivous, inflammatory). Current neuroimaging techniques allow visualisation of the area of the suspected pathology. Some rare causes of PO, such as Tolosa Hunt syndrome with negative neuroimaging findings or ophthalmoplegic migraine remain till now of uncertain classification. Correct approach to the patient requires correlation to clinical data and careful monitoring, to avoid diagnostic mistakes, as the " history" of Tolosa-Hunt syndrome has underlined.

Key words Painful ophthalmoplegia • Tolosa-Hunt syndrome • Ophthalmoplegic migraine

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Introduction

Painful ophthalmoplegia (PO) refers to orbital pain plus any combination of ipsilateral ocular motor palsies, oculosympathetic paralysis (Horner's syndrome) or sensory loss in the distribution of the ophthalmic and occasionally the maxillary division of the trigeminal nerve [1]. It is still worth while for the clinical neurologist distinguishing the different syndromes characterized by PO. Clinical approach to patients with PO. requires extensive differential diagnosis. Four major causes may be identified: trauma, tumors (primary and secondary), vascular and inflammatory disorders (Table 1). However, PO may occur without detectable intracranial lesions as in some cases affected by Tolosa Hunt syndrome (THS) or by ophthalmoplegic migraine (OM), which diagnosis and classification are still now controversial. Extensive reviews have been recently published [1, 2].

Aim of the study

The aim of the study is to review the recent published data on PO, considering 3 main groups: (1) orbital apex syndrome, (2) parasellar syndromes, (3) additional causes, with focus on clinical syndromes of uncertain classification.

Results of the overview

Orbital apex syndrome (OAS)

OAS is a paralysis of all three nerves supplying the external ocular muscles, associated with deficit of the trigeminal and optic nerves. Tipically, the patients present with orbital signs, including proptosis, conjunctival injection, chemosis and resistance to retrodisplacement of the globe. Various orbital diseases

Table 1 Intracranial syndromes causing painful ophthalmoplegia

Topography	Oculomotor nerves (III+ IV+VI) + Other cranial nerves	Syndromes/diseases 1. Trauma 2. Infections 3. Tumours 4. Inflammatory disorders
Orbital apex/ superior orbital fissure	II + V[1]	Superior orbital fissure syndrome
Cavernous sinus /parasellar region	V[1, 2] Sympathetic involvement	Tolosa- Hunt sindrome Reader syndrome
Posterior fossa	VI + V[1, 2, 3]	Gradenigo sindrome

may cause PO; among these, pseudotumor orbitae is a common idiopathic orbital inflammation. The onset is usually acute or subacute, orbital pain is unilateral and exacerbated by eye movements. The disease is steroid responsive [3]. Whether orbital pseudotumor and THS represent identical conditions distinguished only by their anatomical location is unclear [4].

Parasellar syndromes

According to Kline [2], the clinical course is not indicative of the type of lesion causing PO. A gradual onset is not necessarily indicative of a neoplasm, spontaneous or steroid related remission are unreliable in predicting the nature of the underlying process.

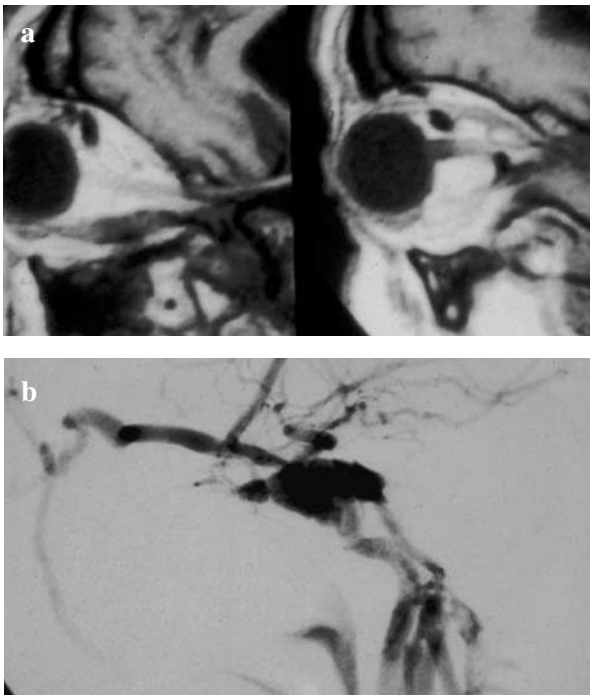

Fig. 1 a,b Mid-sagittal and parasagittal T2 weighted images (**a**) and right internal carotid arteriogram (**b**) in a young patient who experienced abrupt ocular pain, ophthalmoplegia, proptosis and chemosis after a trauma. MRI shows abnormal signal intensity in the region of the right cavernous sinus and ectasic superior ophthalmic vein for unsuccessful drainage into the sinus. Right internal carotid angiogram disclosed a carotid-cavernous fistula

Vascular lesions may cause PO, the more frequent being an intracavernous carotid artery aneurism and carotid cavernous fistula (CCF), at low or high-flow, the first presenting insidiously, the second one with more marked orbital signs (Fig. 1 a,b). THS syndrome has been reported at presentation of CCF [5]. Dissection of the internal carotid artery is a recognized vascular cause of PO. Painful Horner's syndrome is the most common clinical presentation, while ocular palsies are less common. The common *neoplastic* lesions in the cavernous sinus are parasellar tumor (pituitary adenoma, meningioma), perineural or hematogenic spread from distant cancers [6]. Cakirer [7] used MRI to evaluate 23 patients with PO (suspected THS) and found alternative pathologies in 65% of patients (meningioma 17%, pituitary macroadenoma 13%, leptomeningeal metastasis 13%, normal findings 13%). *Infections* may involve cavernous sinus: sinusitis from contiguous region, actinomycosis [8] and tuberculoma [9]. *Inflammatory* causes of PO include those due to a specific systemic disease, such as sarcoidosis, giant cell arteritis, Wegener granulomatosis [10] or systemic lupus erythematousus [11] and those in which PO occurs without systemic signs, such as idiopathic hypertrophic pachymenigitis (IHP) and THS.

IHP is a rare disorder caused by localized or diffuse thickening of the dura [12], THS representing, according to some authors, the localized or self-limited variant [13, 14]. THS is characterized by recurrent unilateral orbital pain with prompt response to steroid therapy. The histopathological studies have showed that it is due to a non-specific granulomatous inflammation of the cavernous sinus [15, 16].

In 1988 the International Headache Society (IHS) classified the THS among the cranial neuralgias [17] defining the diagnosis according to four main criteria. The 1988 IHS criteria have been critized, since pitfalls may derive from their application [18–20]. After cumulating evidence of the role of MRI in the diagnosis [21–23] the criteria have been revised [24] and defined according to five main criteria. The demonstration of granuloma by MRI or biopsy, efficacy of adeguate corticosteroid treatment on both pain and paresis within 72 hours, appropriate investigations and careful follow-up are required for the diagnosis. The application of the new criteria will allow

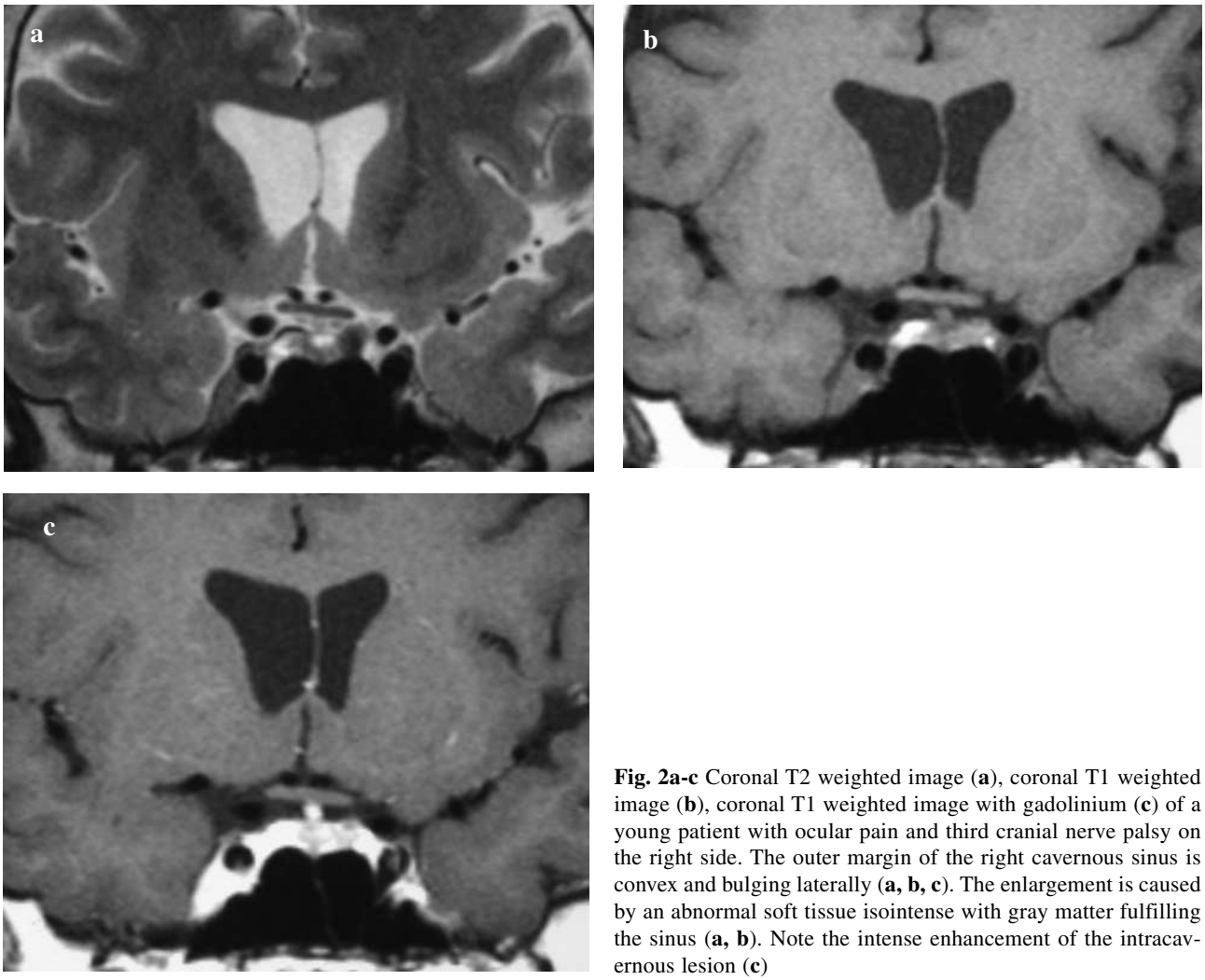

Fig. 2a-c Coronal T2 weighted image (**a**), coronal T1 weighted image (**b**), coronal T1 weighted image with gadolinium (**c**) of a young patient with ocular pain and third cranial nerve palsy on the right side. The outer margin of the right cavernous sinus is convex and bulging laterally (**a, b, c**). The enlargement is caused by an abnormal soft tissue isointense with gray matter fulfilling the sinus (**a, b**). Note the intense enhancement of the intracavernous lesion (**c**)

a better identification of the syndrome, although some aspects need to be clarified, firstly the MRI protocol. At the MRI, the lesion causes an enlargement of the cavernous sinus and appears isointense to the brain tissue on T1 and T2-weighted images with marked enhancement after contrast medium injection (Fig. 2 a-c). MRI findings before and after systemic corticosteroid therapy have been proposed as additional diagnostic criteria [25, 26]. Finally, the relationship between THS and pseudotumor orbitae [4], IHP [13, 14] and multiple cranial nerve palsy syndrome [27] is still not defined, suggesting no progress in understanding the pathogenesis of THS [2].

Additional causes of PO

Diabetic ophthalmoplegia typically produces an acute painful mononeuropathy in a known or previously undiagnosed diabetic person. The recovery usually occurs within 3 months. The episode may be recurrent and partially responsive to corticosteroid therapy.

Ophthalmoplegic migraine (OM) [28] typically occurs in a child or young adult with periodic headache, who develops a oculo-motor nerve palsy (usually the third) at the height of an attack. The paresis lasts for days to weeks after cessation of the headache; recovery is gradual and tends to be less complete after repeated attacks. The finding of enhancement of the oculomotor nerves has suggested its classification among the demyelinating neuropathy [29–31]. The differential diagnosis with THS has been stressed [32]. After the publication of the new IHS criteria, *THS without detectable intracranial lesions* need now a new classification [7, 24].

Conclusions

Clinical approach to PO requires an extensive differential diagnosis, including vascular, neoplastic, infective and inflammatory disorders. Neuroimaging tecniques allow visualisation of the area of suspected pathology. Correct

approach to PO requires correlation to clinical data and careful monitoring to avoid diagnostic mistakes, as the "history "of THS has underlined. Some rare causes of PO, namely THS with negative neuroimaging findings and ophthalmoplegic migraine remain of uncertain classification.

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G. Felisati • P. Lozza • A. Maccari • A. Scotti • M. Leone • G. Bussone

The role of the ear, nose and throat specialist in diagnosing headaches

Abstract The revised International Headache Society classification (2004) represents a very good reference also for ear, nose and throat (ENT) specialists and can be largely shared. The authors follow the classification outline and comment on the chapters of ENT interest. The classification leaves unsolved problems and most of them are of ENT competence, such as mucosal contact point headache. It will be a task for ENT specialists to clarify the real role of very hypothetical primary forms frequently assigned to diagnosis without a correct rationale.

Key words Headache • ENT

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Introduction

The ear, nose and throat (ENT) specialist is frequently consulted when a headache can be caused by an ENT primary disorder. In other cases it is the ENT specialist who diagnoses a concealed form of headache from other symptoms such as in the case of benign paroxysmal childhood vertigo. Sometimes patients are referred to the ENT specialist by their general practitioner, but often it is the patient himself who contacts the specialist, presuming there is some ENT disorder that is causing his headache. For instance, people often assume sinusitis is the most common cause of headache even though they do not have any specific symptoms apart from headache.

ENT literature tends to give more importance to secondary headaches, whereas the revised International Headache Society (IHS) classification (2004) starts with primary forms [1]. Furthermore, strict criteria must be adhered to in order to allow diagnosis of secondary forms [1].

We share the major criteria of the classification and think it is important to speak the same language as other headache specialists, so we will follow the IHS classification, referring only to the disorders of ENT competence.

Benign paroxysmal vertigo of childhood (IHS 1.3.3)

The first chapter of the IHS classification involving the ENT specialist is Migraine, which includes Benign paroxysmal vertigo of childhood.

IHS classification description: this probably heterogeneous disorder is characterised by recurrent brief episodic attacks of vertigo occurring without warning and resolving spontaneously in otherwise healthy children.

Benign paroxysmal vertigo of childhood is quite a frightening rare disease frequently associated with cases of migraine in the family. Vestibular tests are usually normal, setting the child and parents' minds at rest. It usually transforms into migraine in adolescence.

Cluster headache (IHS 3.1)

Cluster headache determines headache attacks with pain and symptoms located in different regions of the face: most of them are typically in the ENT field (nose, cheeks, orbit, eyelid etc.). Cluster includes Sluder's syndrome, although it is also mentioned in Chapter 13: "Cranial neuralgias and central causes of facial pain" where Sluder's sphenopalatine neuralgia is a specific disorder although "not sufficiently validated". For many years ENT specialists have tried to perform various types of medical and surgical local treatments to solve different kinds of clinical conditions that are now included in cluster headaches. The results, not surprisingly, have been very irregular, as the diagnoses and treatments were approximate. Furthermore, the so-called "rhinogenic headaches" were sometimes cured, at least temporarily, by simple treatment, such as touching the nasal mucosa corresponding to pterigo-palatine fossa, with a mixture of drugs.

We have introduced the endoscope to improve the visualisation of the lateral nasal wall site where we inject drugs towards the pterigo-palatine fossa. The preliminary results are quite encouraging, so the endoscopic sphenopalatine ganglion block has now become part of our global treatment protocol for chronic cluster headache, following medical treatment and preceding deep brain stimulation. This last treatment has very good results, but presents very high risks, so it has to be reserved to a limited number of cases.

The secondary headaches

In this chapter we find, among others, all the clinical forms traditionally referred to ENT for diagnosis.

Headache attributed to head and/or neck trauma (IHS 5)

The ENT specialist is only called in here to deal with the dizziness that is usually associated with the headache. He must perform a vestibular test to assess whether a balance lesion is demonstrable and to permit a better clinical and medico-legal evaluation of the patient.

Vestibular suppressor drugs to treat dizziness should be used as little as possible as they tend to delay spontaneous balance compensation. Vestibular rehabilitation is often useful for cases with prolonged dizziness symptoms.

Headache attributed to infection (IHS 9.1)

In headaches attributed to intracranial infection or, specifically, to bacterial meningitis (9.1.1), ENT specialists can be involved for different reasons. Bacterial infection can arise from ENT regions and reach the meninges. The incidence of this illness has decreased in the last 40 years because of generalised antibiotic treatment for all ENT infections, but it still exists. Two different ENT sites generate inflammations that can lead to secondary meningitis: the ear and the nose.

Otogenic meningitis is the most common intracranial complication of neglected otitis media. In the western world such complications seldom occur in children and young adults and are extremely rare in adults and elderly people. The current use of antibiotics and of more sophisticated surgery has greatly diminished the incidence of otogenic meningitis in comparison with the past. This has resulted in physicians having less experience concerning diagnosis and treatment of this complication. Probably due also to high immigration flow in Europe, the incidence of these complications has seemed to increase over the last five years, so a great deal of diagnostic attention is needed. Frequently emergency surgical treatment is mandatory. It is important, therefore, to diagnose the event correctly and to decide on the right treatment.

Meningitis attributed to sinusitis is very rare, but more frequently anterior cranial base dural defects that can provoke cerebrospinal fluid (CSF) leaks and secondary meningitis can be observed. Dural lesions, even those which do not cause an evident CSF leak, must be considered life-threatening as they can cause bacterial meningitis with all its possible complications. It is always vital to detect, localise and repair the dural defect and seal the CSF fistula. ENT involvement in this disorder has two functions: the diagnosis and repair of anterior skull base CSF leaks. Today, the endoscopic transnasal approach is the treatment of choice for these lesions as it has a higher success rate and is less aggressive than the intracranial approach.

Headache or facial pain attributed to disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures (IHS 11)

This chapter is about the secondary headaches typically referred to ENT specialists. It is significant that the IHS classification dedicates only 6 pages to this chapter as they were, in the past, over-diagnosed. In the revised IHS classification, diagnosis of secondary headache is only considered definite when the headache resolves or greatly improves after effective treatment or spontaneous remission of the primary disorder. In the other cases only a diagnosis of headache probably attributed to the cranio-cervical disorder can be applied.

Headache attributed to disorder of ears (IHS 11.4)

Excluding the complications of otitis, like mastoditis and meningitis, which have already been discussed, ear disorders, whether inflammatory or not, seldom provoke either headache or facial pain of any kind together with earache.

If a secondary form is suspected, the ENT specialist has to establish whether or not a primary ear disorder is present. Today many exams can help this diagnosis such as otoscopy, micro-otoscopy, audiometric evaluation, CT scan, etc. As the IHS classification reminds us, in the absence of an ear disorder, the ENT specialist must search for a possible primary lesion site which may create a referred otalgia and headache. If an ear disorder or a referred otalgia is present the ENT specialist must treat and solve the source of the problem.

It is important to remember that to fulfil IHS classification, as for all secondary forms, the headache must significantly reduce or resolve within 3 months of the successful conclusion of the treatment in order to confirm the diagnosis.

Headache attributed to rhinosinusitis (IHS 11.5)

The most frequent cases of headache that the ENT consultant is asked to treat is for patients who believe they are suffering from rhinosinusitis. The concept of sinus disease as a frequent cause of headache is deeply ingrained in the European and American public, but when the ENT specialist visits these patients there is seldom a clear case of sinusitis. In fact, sinusitis is not so common a cause for disabling headache as is generally believed. On the other hand, migraine can cause similar symptoms to rhinosinusitis, such as facial pain, nasal congestion and rhinorrhea. In some clinical studies, 90% of self-diagnosed or physician-diagnosed sinus headaches met the criteria for IHS migraine type headache and migraine treatments helped them [2]. Furthermore, some forms of tension-type headache can simulate frontal sinusitis. Radiological studies demonstrate that sinonasal pain symptoms often fail to correlate with CT findings [3]. However, rhinosinusitis does, in some cases cause headache or can add to other headache forms with an overlap of symptoms. Frequently chronic sinusitis and, in general, nasal disorders are resistant to medical therapy and require a surgical procedure. The ENT specialist must be prudent in assuring the patient that sinus surgery will cure his headache before proceeding, because it is not certain that rhinosinusal normalisation will heal headache, as it may have a different cause to sinusitis.

Rhinosinusitis only causes pain when inflammatory congestion closes the sinusal ostia, causing a closed circuit with further inflammation and pneumatic pressure that tends to maintain active sinusitis even when the nasal cavities seem clear. Chronic sinusitis does not usually cause facial pain or headache, but when it relapses into an acute phase it can do so. Endoscopic rhinosinusal examination is needed to confirm suspected sinusitis. On the basis of the endoscopic evaluation, the ENT specialist can decide if it is necessary to perform a medical treatment. Endoscopy permits the specialist to follow up the patients and to execute laboratory investigations or radiological examinations when needed. IHS classification, correctly, does not indicate the old radiological exams as useful for the diagnosis. Nowadays if we want more information with respect to what endoscopy can give us, we need to perform a CT scan or MRI.

Headache attributed to other disorders of cranium, neck eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structures (IHS 11.8)

This appears to be a chapter in which the IHS classification wants to insert all the lesser established or lesser known secondary forms that are characterised by a precise causal relationship with a hypothetical primary disorder and which recover after the treatment of the primary form.

Cranial neuralgias, central and primary facial pain and other headaches (IHS 13)

This big chapter includes some well known neuralgias and a lot of minor forms of facial pain that can refer to ENT. Usually the ENT specialist has only to control the absence of a primary form in the upper aero digestive tracts: special attention must be paid to tumours. Rhinofibroscopy, a very well tolerated exam, consistently helps the diagnosis.

Glossopharyngeal neuralgia (13.2)

A patient with a glossopharyngeal neuralgia can consult an ENT specialist or, more frequently, an ENT specialist is asked by the general practitioner or the neurologist for a clinical evaluation. The form is quite rare and the correct diagnosis must exclude ENT primary forms.

Nervus intermedius neuralgia (13.3), Superior laryngeal neuralgia (13.4), Nasociliary neuralgia (13.5), Neck-tongue syndrome (13.9), Persistent idiopathic facial pain (13.18.4), Burning mouth syndrome (13.18.5)

In these small chapters the classification inserts some rare forms whose existence is frequently discussed, but for which specific description and validation are believed sufficient. The disorders that concern ENT are reported here. Any single form is open to discussion. It is difficult to affirm that nasociliary neuralgia is a specific form in a defined chapter, and at the same time, sustain that the classic Sluder's sphenopalatine neuralgia is not sufficiently validated. The different handling of these two diagnoses is probably due to the fact that in nasociliary neuralgia the trigger point is on the face, while in Sluder's sphenopalatine neuralgia it is

inside the nose, so more difficult to assess. In the old classification both were included in Cluster forms. Here again the ENT specialist is required to point out the absence of a potential ENT primary form.

Other cranial neuralgia or other centrally mediated facial pain (13.19)

This chapter refers to three rare forms that are not believed to be sufficiently clarified and validated, but that are traditionally mentioned among the forms of facial pain: Vail's Vidian neuralgia, Sluder's sphenopalatine neuralgia and Eagle's syndrome. Even today many ENT or maxillofacial specialists make these diagnoses. See the previous chapter for some discussion of this.

Appendix

Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures (IHS A11), Mucosal contact point headache (A11.5.1)

The appendix includes a chapter that is of paramount importance for the ENT management of headaches: mucosal contact point headache. The revised IHS classification differentiates between this condition and septal deviation or turbinate hypertrophy. It does not consider either of the latter conditions sufficiently validated. We feel this is an error in the classification because mucosal contact only exists when the contact is determined by deviation of the nasal septum and/or hypertrophy of the turbinates.

It is well known that among people with nasal disorders, headache has a higher prevalence with respect to people without any nasal obstruction. At the same time it is verified that among people with headache, nasal disorders have higher prevalence with respect to normal. So a link between these two disorders surely exists. In the past ENT medical and surgical treatment for the management of "rhinogenic headaches" has been used frequently. Some of these treatments did not have any proven rationale. However, sometimes an ENT surgeon observes that, after surgery for septal deviation and/or middle-inferior turbinate hypertrophy, a chronic headache abruptly disappears. In our experience it happens only occasionally. Looking at the literature, contrasting opinions can be observed. Some authors report very good surgical success for mucosal contact point headache, but generally a small number of patients is analysed. On the other hand, Abu-Bakra and Jones [4], studying a large number of patients attending a rhinology clinic (973 cases) found that the prevalence of nasal mucosal contact point was the same (4%) in the groups with or without facial pain. They conclude that: "surgery undertaken to remove mucosal contact points for facial pain is usually unnecessary as the aetiology of this facial pain appears to be a more central process" [4]. This report, anyway, is not completely convincing, as the total number of patients with facial pain (4%) seems too small in this study. We agree with the IHS classification that this is an open subject.

However, many of these patients have real nasal problems together with headache, so nasal surgery is frequently necessary. The surgeon cannot assure a cure for headache, but only the improvement of nasal obstruction; if the headache disappears, it will constitute a great success. It is not correct to perform very aggressive interventions on the basis of an unproved rationale, but it is mandatory to adopt the modern concepts of mini-invasive nasal surgery. If headache is the only symptom and no other pathogenesis is observable, but mucosal contact points are evident, the surgeon is up against a dilemma.

Conclusions

The revised IHS classification (2004) represents a very good reference also for ENT specialists and can be largely shared. It leaves unsolved problems and most of them are of ENT competence, such as mucosal contact point headache. It will be a task for ENT specialists to clarify the real role of very hypothetical primary forms frequently assigned to diagnosis without a correct rationale. For these reasons, the IHS requires that any diagnosis of a secondary form is possible only when there is a clear relationship between recovery from the primary form and cure or great reduction of headache. Clearly this is a great limit when the primary form is not easy to treat or may require surgical intervention. In such cases headache, according to the IHS classification, can be coded as "headache probably attributed to [the disorder]" and the surgeon must pay great attention to ensure the patient is aware that surgery may not be a cure for the headache.

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KEY NOTE LECTURE

F. Andrasik • H. Flor • D.C. Turk

An expanded view of psychological aspects in head pain: the biopsychosocial model

Abstract Traditionally, headache has been viewed from a limited perspective, both medically and psychologically. The authors propose that a more expanded view of headache that considers each perspective as important, as embodied in the biopsychosocial model, will greatly enhance understanding and be more useful in treatment planning. This model views pain as emanating from a complex interaction of biological, psychological and social variables. This paper describes the key behavioural, affective and cognitive influences and provides pertinent supporting examples from the literature.

Key words Biopsychosocial model • Headache • Atypical facial pain • Affect • Cognition

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Introduction

The prevailing model to account for all forms of chronic pain, including headache, facial, and atypical facial pain, is best termed as the "biomedical model," and it is characterised as viewing pain as a direct transmission of impulses from the periphery to structures within the central nervous system [1]. As concerns headache, this model has led to a number of important insights into pathophysiological mechanisms and development of pharmacological treatments directed at modifying aberrant aspects. At the same time, this model has a number of limitations and has difficulty explaining the following: (1) pain that continues in the absence of identifiable pathology, (2) pathology that exists in the absence of pain, (3) the markedly varied individual responses to identical treatments, (4) the failure of potent medications to provide consistent pain relief, and (5) the absence of a strong relationship between pain, impairment and disability [1]. Some dismiss such limitations, attributing them to inadequate technology and claiming that these issues will be resolved in due time. Yet, an alternative viewpoint is that varied psychological factors play an important role in the genesis, exacerbation and maintenance of recurrent pain conditions and a proper explication of these factors can aid in understanding and ultimately treatment.

Early psychological models of pain and headache were unidirectional, oversimplified (e.g., pain in the absence of identifiable pathology was judged either to be motivated for secondary gain or was believed to be maintained by reinforcement contingencies), and had minimal impact upon the field. This view, like the biomedical model, also perpetuated an artificial dichotomy, that pain was either somatogenic or psychogenic [1]. A model that is more fruitful and heuristic is that which has been labelled the "biopsychosocial" or "biobehavioural" model (in the latter case, behavioural subsumes psychological and social factors). This model views pain (and any chronic illness) as emanating from a complex interaction among biological, psychological and social variables. From this perspective

[1] the diversity in illness expression (including severity, duration and consequences to the individual) can be accounted for by the complex interrelationships among predispositional, biological and psychological characteristics (e.g., genetics, prior learning history), biological changes, psychological status, and the social and cultural contexts that shape the individual's perceptions and response to disease. This model stands in sharp contrast to the traditional biomedical perspective that conceptualises disease in terms of more narrowly defined neurophysiological dimensions. This alternative model differs in other key ways, as it is dynamic and recognises reciprocal multifactorial influences over time. The text to follow expands further upon this more integrative model and provides some illustrative examples that demonstrate the psychosocial influences. Other papers within this series address biological influences, so these are not addressed further here.

For purposes of discussion, the psychosocial aspects are divided into the categories of behavioural, affective and cognitive influences.

Behavioural

The behavioural realm may be further subdivided into three types of learning: nonassociative, associative and social. Important processes to consider for nonassociative learning, but ones that are typically ignored when considering development of chronic pain, are habituation, defined as a decrease in the intensity of a response when the same stimulus is repeatedly presented, and sensitisation, defined as an increase in the intensity of a response when the same stimulus is repeatedly presented [2]. Patients who have continuous pain show sensitisation when exposed to painful stimuli, while nonpain patients (and patients with pain that is episodic) reveal habituation [3].

Associative learning consists of operant and respondent conditioning, with the former being studied most intently. Fordyce [4] was the first to comment on the role of operant learning regarding pain patients, pointing out how acute or episodic pain could develop into a more chronic form with attention from significant others including health care providers. He also noted how medication consumption, inactivity or avoidance of undesirable activities could be negatively reinforced (by terminating unpleasant states) and how well behaviours could concurrently decrease due to a relative lack of reinforcement. Research with chronic pain patients supports these basic tenets. For example, a number of studies have shown that pain patients exhibit more pain behaviour and report increased pain in the presence of solicitous spouses *vs*. the presence of more neutral parties and *vs*. controls [2]. Gentry and Bernal [5] have similarly pointed out how respondent conditioning can influence pain. Their model begins with the observation that acute pain (the unconditioned stimulus) is associated with sympathetic activation and increased muscle tension (the unconditioned response). With repeated pairings, stimuli that were previously neutral (environmental characteristics, body position, termed the conditioned stimuli) now come to elicit fear of pain and the sympathetic activation and the increased muscle tension mentioned before (now the conditioned response). Once established, the pain-tension cycle and anticipatory fear of pain may continue even in the absence of the original tissue damage [see also 6].

Finally, many responses are learned by observing and imitating the behaviour of others, and this is true for the expression and localisation of pain and ways of coping with pain [7, 8]. As a few examples, patients with solicitous spouses provide higher ratings of pain [9], reveal poorer performance on treadmills [10], and have lower pain thresholds and pain tolerance [11] when they believe they are being observed *vs*. not being observed. In a related fashion, pain patients are more likely to respond to marital conflict situations with increased pain behaviours [12]. Intervening in this realm can be complicated because these behaviours can serve adaptive functions [11]. Finally, even facial expressions can alter reports of pain [13].

Affective

The International Association for the Study of Pain [14] defined pain thus: "It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an emotional experience." There is no doubt that pain and negative affectivity (anxiety, depression and anger) go hand-in-hand [15–17]. Knowledge of this leads to a simple question, "how does affect interact with pain?" Although it is asked simply, the answer is not nearly so easily provided. Fernandez [17] points out there are six primary models to consider in addressing this question: affect as a (1) correlate of pain, (2) predisposing factor, (3) precipitating factor, (4) exacerbating factor, (5) consequence and (6) maintaining factor. Which one (or ones) best applies to a given patient has a direct bearing on the treatment that might be selected (as outlined in Table 1).

Fernandez [17] discusses methodological aspects that warrant consideration in future investigations and consideration of which might provide further important insights. These concern study of expanded affective types or newly recognised diagnostic entities, a greater focus on individual symptoms, consideration of complications due to Berkson's Paradox [18] (the spurious association that is observed because persons with two or more disorders are more likely to enter treatment than an individual with one disorder), greater attention to potential biasing factors (co-occurrence as an artefact of overlap in diagnostic criteria or measures, point of diagnosis *vs*. point of onset, etc.), and more careful attention to sample source.

Table 1 Treatment suggestions based on operative affect model (adapted from [17])

Affect as	Treatment approach
Predisposer	Characteriological change
Precipitant	Short-term intervention for affective trigger itself
Exacerbator	Focused intervention to defuse the aggravator
Perpetuator	Alter environmental conditions maintaining the pain
Consequence	Provide minimal attention to affect
Correlate	Third superordinate factor may be responsible; look elsewhere
Reciprocal relationship	Target both

Cognitive

Melzack's Neuromatrix Theory of Pain [19] proposes that a variety of cognitive factors can play a significant role in the experience of pain. Among these are attention, coping styles, beliefs, expectations, and memories about pain [20]. There is a growing literature suggesting that individuals who experience recurrent pain have an attentional bias that leads them to be over-responsive to pain-related stimuli [21]. Pain interrupts and demands attention, because it is an alarm signal for action [22], and this may be especially so for people with a high level of fearfulness about pain [23]. Studies employing high-resolution functional magnetic resonance imaging have shown that focusing attention on pain leads to activation in the periaqueductal grey region, whereas distraction leads to decreased activation in several areas involved with pain regulation (thalamus, insula and parts of the anterior cingulate) [24, 25].

The way people cope with pain has a bearing on the experience of pain. Consider for example the negative approach of catastrophising, which involves rumination about an aversive or negative event that is accompanied by a magnification of the extent of the problem and an attendant feeling of helplessness. Catastrophising is widely linked to chronic pain, particularly the subjective experience of pain [26] and this has been found in headache patients [27]. Headache patients tend to use other maladaptive strategies for coping (withdrawal, avoidance, self-criticism) as well [26, 28]. Another strategy, acceptance which is characterised by a state of remaining in touch with one's feelings and thoughts without making an active effort to change or attend to them, has been shown to be related to lower levels of pain, avoidance, depression and disability in patients who suffer from chronic pain [29–32].

Beliefs, appraisals and expectancies held by patients regarding possible consequences of pain and their abilities to deal with them can impact functioning both directly (by influencing mood, which can in turn affect muscle tension and biochemical processes) and indirectly (by altering attempts to cope) [2]. Beliefs can even affect pain severity. Newton and Barbaree [32] sampled the thinking of headache patients during and following a headache episode, both before and after treatment. Compared to the untreated control group, the treated group revealed a reduction in negative appraisals ("the headache is getting worse"; "there is nothing I can do") and a corresponding increase in positive appraisals. The authors noted that patients who reported the greatest shift in positive appraisals obtained the greatest reductions in headache activity. Further, intense pain was associated with more negative appraisals of headache episodes.

A laboratory study provides evidence that expectation alone can produce head pain. In this investigation, Bayer et al. [33] led participants to believe they would receive an undetectable current, which was "safe but often painful", applied to the forehead to measure the effect upon reaction time. Over one-half of the participants reported experiencing a headache and the reported pain level was in direct proportion to the displayed intensity setting.

A related concept is self-efficacy, or beliefs regarding a person's ability to engage in action that can influence the outcome of a headache episode. Headache self-efficacy beliefs (as assessed by the Headache Specific Self-Efficacy Scale [34]) have been shown to be related to positive coping responses, active efforts to manage and prevent pain, and increased pain tolerance. Self-efficacy can also mitigate the relationship between stress and headache; as self-efficacy increases, the correlation between headache and stress decreases [35]. Bandura and colleagues [36] have demonstrated that self-efficacy beliefs can activate opioid-mediated pain inhibitory mechanisms and increase pain tolerance.

Finally, patients are more likely to remember pain when they are in a pain state [37, 38] and they focus on pain when asked to report life experiences in autobiographical memory tasks [39]. These memory processes may lead to a selective focus on stimuli that have been associated with pain in the past, which in turn can lead to avoidant behaviour. Further, activation of painful or stressful memories can instigate physiological arousal, along with hypervigilance [2]. Thus, merely thinking about pain [40], discussing painful experiences [41] or observing others performing activities that

patients themselves are fearful of [42] can lead to increases in muscle tension, heart rate and skin conductance.

Thus, all forms of recurrent pain, including typical and atypical facial pain, are influenced by a number of interacting factors, biological and psychosocial. The most complete understanding will be obtained by incorporating a biopsychosocial viewpoint.

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Pharmacological therapy of atypical facial pain: actuality and perspective

Abstract Atypical facial pain is a condition, which creates a difficult challenge for every physician, either for diagnosis or for choice of treatment. There are very few controlled studies and evidence-based data about what constitutes the gold standard treatment. Most physicians treat this condition with antidepressant agents, thinking that the psychiatric aspects, often present in these patients, play a fundamental role in the pathogenesis of the condition. However, antidepressant drugs are effective also in non-psychiatric patients, and new compounds, with no effect on psychological aspects, have recently seemed to show good activity in controlling pain in this disorder. We review the different possibilities available for treating this frustrating condition.

Key words Atypical facial pain · Atypical neuralgia · Atypical pain · Chronic pain

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Atypical facial pain (AFP) represents a very difficult and complicated challenge for every physician, either regarding nosography or clinical aspects [1–4].

Before choosing between different treatment options, we have to recall how important it is to rule out organic diseases as a cause of atypical pain. In the literature there are several reports that describe neoplasm, arterio-venous malformations and chronic inflammatory diseases (such as tuberculoma or granuloma) that produce an "atypical" pain in the face. The main sites where these pathological processes are localised are the brainstem, the ponto-cerebellar angle and the cavernous sinus, but there are observations of diseases affecting different and more distant regions of the body, like latero-cervical regions and apical lung.

After excluding an organic disease, facial pains can be divided in two categories: neuralgic – or neuropathic – and non-neuralgic pain [5]. The former type of pain may be *acute* or *chronic*. Acute neuralgia represents the "typical" pain, the pain of the trigeminal neuralgia. Vice versa, chronic neuralgiform pain is considered "atypical", mainly because it lasts longer than the few seconds of trigeminal typical pain. Non-neuropathic pain is characterised by "myofascial" pain, but the pathogenetic mechanism of this kind of ache is not clear, with the possibility of psychogenic-functional aspects playing an important role.

The definition "atypical facial pain" is currently used for neuropathic chronic and for non-neuropathic pain. In this way, the term is comprehensive of all those syndromes that are not caused by organic diseases of the cranio-facial structures and that do not have the clinical presentation of "typical" pain (i.e., brief electric shock-like pains, strictly limited to the distribution of a nerve, pain evoked by trivial stimuli etc.).

The therapeutic approach to AFP is strongly conditioned by the little knowledge that we have in the nosographic and pathogenetic fields. In the past, therapies starting from aetiopathogenetic theories have never been successful. This is not the case of tricyclic antidepressants,

even if the efficacy was probably not due to a purely antidepressant effect.

Tricyclic antidepressants, especially amitriptyline, represent the first choice treatment for these disorders [6, 7]. Their use was suggested because many patients shared depressive features and facial pain. Moreover, among the different hypotheses there was the theory that considered AFP to be the result of a conversion disorder or a psychosomatic complaint. However, there is evidence of efficacy independent from the antidepressant effect: good responses at low doses, efficacy on patients without psychiatric problems, onset of action shorter than antidepressant effect, etc. It is possible that the pharmacological properties of the drug, especially the serotonin reuptake inhibition, the direct action on serotoninergic, adrenergic, cholinergic and hystaminergic receptors, may be relevant for the therapeutic effect. Moreover, amitriptyline potentiates the activity of endogenous opiates and seems to antagonise NMDA receptors.

Recently, it has been demonstrated that amitriptyline reduces nociceptive discharges starting from myofascial tissues, giving a reason for the control of chronic pain originating in these structures.

The therapeutic range usually employed is 25–100 mg, taken in a single dose at bedtime. Treatment must be continued for several months and, once stopped, has to restart if pain arises again.

Non steroid anti-inflammatory drugs (NSAIDs) are often used to treat these conditions. Their use must be carefully evaluated: when taken for long time, side effects are serious and often non-reversible. Using NSAIDs for a short period may be a better choice, when there is an exacerbation of symptoms or when pain has begun a few days or weeks ago.

A lot of other compounds have been employed to treat this pain, but controlled studies are not enough to consider these drugs useful in the treatment of facial pain. In recent years, anticonvulsants have been largely used, mainly gabapentin, clonazepam, lamotrigine, phenytoin and valproic acid. No clear data about the efficacy of these drugs have been produced. Other agents used include baclofen, β-blockers, different antidepressants, calcitonin, sumatriptan and intranasal cocaine.

A recent review [8] on chronic pain in facial regions (because of temporomandibular disorders (TMD), AFP and burning mouth syndrome) analysed 11 studies out of 89 randomised clinical trials. Only 2 trials were conducted with AFP patients, and 3 other studies with mixed groups of patients with TMD and AFP. In the 2 studies with AFP patients only, in one calcitonine was no better than placebo (with a small group and a high drop-out rate) and in the other sumatriptan was found to be significantly superior to placebo. The other 3 studies analysed the effect of amitriptyline, dothiepine and intranasal cocaine, finding that all these drugs were superior to placebo in patients with AFP or TMD.

A more recent study [9] evaluated the efficacy of venlafaxine in 30 patients with AFP. Only 20 patients completed the study: there was no difference in pain intensity, measured by visual analogue scale, between the baseline and the end of the treatment period, whilst there was a significant decrease in the use of rescue medications, and also pain relief, measured by a verbal rating scale, was statistically significant.

Regarding non-pharmacological treatment, there is no indication for surgical procedures, which could be not only unnecessary but even dangerous and could aggravate the pain [10]. A “peripheral” approach can give relief, with injections of local anaesthetic and steroids, especially when the local component of pain is significant. Other treatments that have been proposed are TENS, biofeedback and acupuncture, but data available for these techniques are not sufficient to justify their use in daily activities.

Finally, a questionnaire about the diagnosis and the best treatment of AFP [11] has been sent to 240 UK specialists (of different fields, all dealing with AFP): 78% of the specialists used antidepressants (3/4 tricyclics) as first choice treatment. The other specialists used anticonvulsants as first choice drug. Second choice and alternatives to these compounds consisted of many drugs and techniques, the most used being NSAIDs, benzodiazepine, psychiatric help and physiotherapy. Nineteen specialists stated they kept these patients under observation without treatment.

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The role of surgery in the treatment of typical and atypical facial pain

Abstract Effective management of facial pain syndromes requires a correct clinical diagnosis. The temporal pattern of chronic pain is the most important aspect to be considered. It allows the identification of three groups of patients: (1) those who have paroxysmal pain, (2) those with mixed paroxysmal and constant pain, and (3) those with strictly constant pain. The less is the paroxysmal component, the more likely it seems to be that surgical intervention is useless or even dangerous. In particular, when the diagnosis is atypical facial pain, that is, a diffuse, nonanatomic orofacial pain of unknown pathophysiology, none of the surgical strategies that can cure trigeminal neuralgia should be used. Trigeminal neuralgia patients are often referred to neurosurgeons because of their well-known capability to obtain pain relief through many different procedures such as microvascular decompression, percutaneous balloon microcompression, thermorizotomy, drug injection within the trigeminal cistern and radiosurgery. Since all these procedure can cure patients with typical trigeminal neuralgia, the ideal algorithm of treatment is still under debate. We report on our 20 year-long experience with the surgical treatment of facial pain in general and trigeminal neuralgia in particular. Our treatment algorithm for trigeminal neuralgia is presented. Some ideas to offer a possible surgical help to patients with less typical, medically intractable, chronic facial pain are also given.

Key words Atypical facial pain • Trigeminal neuralgia • Surgical treatment • Radiosurgery • Deep brain stimulation

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Introduction

Facial pain remains a field in which the diagnostic capability of the treating physician makes a big difference to the outcome. In most cases, in fact, the patient's history is the most important aspect of the diagnostic evaluation. The symptom of facial pain can be quite specific and diagnostic if an accurate description of its temporal pattern and characteristics is obtained. Three groups of patients can be identified: (1) those who have paroxysmal pain, (2) those with mixed paroxysmal and constant pains and (3) those with strictly constant pain. The more paroxysmal pain dominates the patient's complaint, the more likely it is that surgical intervention may help.

Trigeminal neuralgia (TN) is an uncommon disease (incidence 4.7/100 000) characterised by attacks of recurring, paroxysmal, shock-like pain within the distribution of one or more branches of the trigeminal nerve. Light tactile stimulation may trigger such an attack. Clinical features of TN have been well known since the first description by Fothergill in 1773 and many different surgical treatment modalities such as trigeminal nerve sectioning and injection of chemical agents have been applied. Most of them have only historical value. Nowadays the neurosurgical armamentarium includes more traditional treatment options, either percutaneous such as radiofrequency thermorhizotomy (TRZ) and balloon microcompression, or open such as microvascular decompression (MVD), along with novel radiosurgical techniques. Because all these treatment options seem to have a good success rate with low risks, the ideal algorithm of treatment is still under debate. The authors report on their experience in the treatment of TN. Their own treatment algorithm is also presented.

Facial pain is described as atypic when a diffuse, nonanatomic orofacial pain of unknown pathophysiology is present. This diagnosis should be made only in the following conditions: (1) when other aetiologies for facial pain have been first considered, evaluated and excluded, (2) when objective evidence for other facial pain syndromes is lacking,

(3) when specific antecedent psychological or behavioural factors can be identified. Although in very strictly selected cases surgery able to modulate the function of the descending antinociceptive pathways through either cortical or deep brain stimulation may be a treatment option, surgery aiming to create a lesion on both central and peripheral nervous system is absolutely contraindicated.

The surgical treatment of trigeminal neuralgia

Even though new drugs have been recently introduced in the treatment of TN [1, 2], about half of all patients eventually require surgery for pain relief. Drug resistance or drug intolerance can be in fact commonly observed in patients with a long history of disease. Many different surgical treatment modalities such as trigeminal nerve sectioning and injection of chemical agents have been applied. Most of them have only historical value. Three are the well-consolidated techniques that have been used on thousands of patients all over the world and that should be considered when a patient requires surgery for pain control: MVD, percutaneous TRZ and percutaneous balloon microcompression (PBM). Radiosurgery can be an option whose results are more unpredictable and still under evaluation.

Microvascular decompression

Although controversies still exist about the role of vascular compression in the pathogenesis of TN [3–5], MVD today represents one of the most widely used surgical options for this painful condition. Several studies agree on the high rate of long-term efficacy. Our experience with MVD started in 1990 and so far 563 patients, including 38 patients affected by multiple sclerosis (MS) have been operated upon. All patients who did not want to experience any sensory disturbance underwent this kind of surgery as the first option. Advanced age should not be considered as a contraindication if a mininvasive technique is used.

Results and prognostic factors

At long-term follow-up (0.5–13 years, mean 4.5 years) 76% of patients were found completely pain-free without medication, 5% were found pain-free with a dosage of drugs lower than in the pre-operative period and 15% required repeated surgery or high dosage of drugs. We were unable to follow-up 4% of patients. The outcome in the MS group was worse with only 39% of patients completely pain-free without medication at long term follow-up and an additional 5% reporting no pain with low dosage, sporadic assumption of drugs. Despite the high recurrence rate, these results show that a generally considered contraindicated surgery can achieve excellent results in some MS patients. Unfortunately, however, we were not able to find any prognostic factor that might allow for a better selection of surgical candidates [6]. A statistical analysis of the "essential" TN group was used to relate likelihood of post-operative recurrence of tic to the following variables: patient's age and sex; involved side and branch; duration of symptoms; history of previous trigeminal ablative procedures; kind of neurovascular conflict (arterious, venous or both); post-operative numbness; hypertension. A long duration of clinical history (>84 months) was found statistically associated to a worse outcome ($p<0.05$). No other statistically significant prognostic factor could be identified [7].

Table 1 MVD: mortality and long-term side effects

Author(s)	Patients	Mortality	Cereb Inf	Def VIII	Def VII	Dipl	Def V	PD
Taarnhoj (1982) [39]	350	2 (1.1%)	0.3%	1.4%	0.6%	0.3%	0	0
Barba and Alksne (1984) [40]	37	0	0	0	0	0	5%	0
Zorman and Wilson (1984) [41]	125	0	0	3%	0	0	0	0
Szapiro et al. (1985) [42]	70	1 (1.43%)	1.4%	0	0	0	0	0
Bederson and Wilson (1989) [43]	252	2 (0.07%)	0	3%	0	0	0	0
Dahle et al. (1989) [44]	57	1 (1.7%)	0	0	0	0	1.7%	1.7%
Sindou et al. (1990) [45]	60	0	0	0	0	0	0	0
Klun (1992) [46]	220	3 (1.3%)	0	0.4%	0	0	0	0
Sun et al. (1994) [47]	61	0	0	1.5%	0	0	1.5%	1.5%
Meneses et al. (1995) [48]	50	0	0	0	0	0	0	0
Pamir et al. (1995) [49]	32	0	3%	0	0	0	0	0
Mendoza and Illingworth (1995) [50]	133	1 (0.7%)	1.4%	0	0	0	0	0
Barker et al. (1996) [51]	1336	2 (0.2%)	0.1%	1%	0	0	0	0
Present report (2005)	563	1 (0.2%)	1 (0.2%)	0.6%	0	0	0.8%	0

Cereb inf, cerebellar infarct; *Def*, deficit; *Dipl*, diplopia; *PD*, painful dysaesthesia

Surgical technique and side effects

Exploration of the cerebello-pontine angle is performed in the supine position through a 5-cm skin incision that allows for a small (less than 20 mm in diameter) key-hole retromastoid craniectomy. After dural opening, the fifth cranial nerve is exposed and examined microsurgically for vascular compression through a supracerebellar approach. The nerve is then cautiously dissected free from the offending vessel without unnecessary manipulation.

In our series no major permanent morbidity was recorded. Ataxia, disequilibrium and gait disturbances sometimes were found in the early post-operative period. Collecting data from the literature series on more than 3000 published cases, the mortality rate is 0.3% [7]. Cranial nerve morbidity is reported, but generally diplopia, dysphagia, facial weakness, vertigo and trigeminal hypoaesthesia are rare and always transient. Injury to the acoustic branch of the VIII cranial nerve is the only relevant long-term cranial nerve dysfunction reported in several series, ranging from 0.1% to 3% (Table 1). This is probably the only complication that cannot be prevented in all cases because of the extreme vulnerability of the internal auditory artery and its cochlear branches. In our hands switching the approach from laterocerebellar to supracerebellar reduced the manipulation of the VII–VIII cranial nerve complex and the incidence of this complication from 1% to 0.4%. Other reported complications such as CSF leakage, haemotympanum, sigmoid sinus thrombosis, cerebellar infarct and haematoma can be reduced in incidence with a careful surgical technique and perfect haemostasis. We did not find any age-related statistically significant difference in incidence of surgical complications and so we perform MVD without an absolute age limit.

Aetiopathogenetic considerations

A peripheral hypothesis [8, 9], a central hypothesis [10] and more recently, theories supporting central–peripheral hypotheses [11, 12] on TN aetiopathogenesis have been proposed. Nevertheless it remains a puzzling mystery. Both trigeminal nerve lesions and central lesions affecting trigeminal pathways (MS, ischaemia) [13, 14] have been reported to play an aetiopathogenetic role in TN. Vascular cross-compression is now increasingly accepted as an important aetiological factor. We found a vascular conflict in most cases, even in patients with MS. It is possible that demyelination of trigeminal fibres at the level of trigeminal root entry zone in the case of vascular cross compression [8, 9, 11, 15–17] and demyelination of the trigeminal pathways within the brainstem in the case of MS may result in abnormal ephaptic transmission of impulses. Vascular conflict (and possible consequent demyelination) and MS demyelination were found to coexist in some cases and possibly cooperate in the genesis of painful attacks. The classic distinction between the supposed "all central" mechanism for MS-associated TN and the "all peripheral" mechanism for the vascular compression-related TN should therefore come under reconsideration. In its place we offer a unique (TN-MS patients are included), mixed central–peripheral mechanism in which abnormal impulses arise from demyelinated axons (MS, vascular compression and any other possible cause of demyelination along the central and the peripheral course of trigeminal axons) and modulate nuclear activity. Minimum myelin damage, without any nerve hypofunction, might be involved in the aetiopathogenesis of idiopathic TN [10]. Major myelin damage may be responsible for MS-associated TN based on the finding of possible clinical signs of trigeminal nerve hypofunction [14], MRI signs of demyelination, and, unfortunately, by the recurrence of pain after MVD. The concept of a central neuromodulatory role of impulses coming from the area of cross-compression also explains the possibility that a long-lasting alteration of discharge modalities of the trigeminal root can cause lowering of the pain threshold as suggested by recent reports on extracranial neurovascular conflicts [18, 19].

If this mixed peripheral–central hypothesis appears to be compatible with our [7] and others' [20] apparently contradictory findings in TN, an alternative all-central hypothesis might also be considered. Supporters of this all-central mechanism deny any pathological role for vascular compression. According to this view, MVD elicits pain relief because it produces a sufficient trauma, which then interferes with normal nerve functioning which then dampens the abnormal brainstem activity responsible for TN [3]. In our series we were not able to identify any prognostic factor. In particular, no statistically significant difference in the outcome between patients with severe *vs*. mild conflicts was found, which we believe adds further emphasis to the major role played by central mechanisms in patients with MS-related TN.

However, MVD certainly interferes with the pathological impulses that arise in the region of demyelination induced by chronic vascular cross compression and even if it could not be considered as the "definitive aetiological cure" [21], it is the only therapeutic option able to obtain pain relief without causing any sensory disturbance.

Thermorhizotomy

TRZ became one of the most used surgical procedures for the treatment of TN after its introduction by Sweet and Wepsic in 1974 [22]. In the following years, experimental data supporting the effectiveness of TRZ for the differential destruction of small diameter nerve fibres were reported [23, 24] and its efficacy has been confirmed by many authors in large series of patients [25–29]. TRZ allows the majority of facial touch sensibility to be spared, and hypalgesia or analgesia generally involve only the targeted trigeminal branches. More than 1700 patients have been so far treated at Istituto Nazionale Neurologico Carlo Besta since 1974. We were able to follow-up 97% of patients for a time ranging from 2 to 15 years (mean follow-up 72 months) (Table 2). Regarding the amount of the inflicted sensory deficit, our data suggest

Table 2 PMC and TRZ for TN: long-term results

	PMC	TRZ
Completely pain free without medication, %	58	71
Requiring low dosage of drugs, %	12	11
Requiring high dosage of drugs or surgery, %	30	15
Painful anaesthesia, %	0	1.5
Requiring drugs for dysaesthesia, %	4	5
Permanent diplopia, %	0.4	0.5
Keratitis, %	0	0.5

that patients with post-operative hypalgesia have a pain recurrence probability of 41% *vs*. 7.5% for patients with post-operative analgesia. In other words, induced post-operative analgesia prevents the recurrence of pain in most patients. In all patients the sensory deficit tends to diminish with time. Complications such as severe dysaesthesia and painful anaesthesia are clearly related to the technique itself and cannot be completed avoided even with meticulous surgical technique. The total percentage of patients who required drugs for severe dysaesthesia was 5%, with 1.5% of painful anaesthesia that we were never able to definitively alleviate by any of the more advanced surgical antalgic techniques (open or percutaneous trigeminal tractotomy, trigeminal stimulation, cortical stimulation, deep brain stimulation, CSF direct drug infusion).

Major ocular deafferentation complications can generally be avoided by monitoring the corneal reflex during the procedure. Keratitis requiring tarsorrhaphy was observed in only 0.5% of patients even if the involvement of first branch was not considered as a contraindication to this kind of surgery. Masseter weakness with minor chewing impairment appeared in 10% of patients, ocular palsy and diplopia in 0.5%. Major neurological morbidity due to intracranial bleeding was never observed. Mortality was null. This method can be proposed to patients accepting the risk of sensory disturbances when previous less aggressive procedures have failed.

Balloon microcompression of the Gasserian ganglion

The simple concept that deliberate direct compression of the trigeminal ganglion can relief trigeminal pain [30], led Mullan and Lichtor in 1978 to develop a percutaneous technique for controlled compression of the trigeminal ganglion [31]. The results that we were able to obtain by using balloon microcompression of the Gasserian ganglion (PMC) in 235 patients operated upon since 1992 are reported in Table 2. The endpoint for compression was the achievement of a "pear" shape balloon in the cavum Meckel. The balloon is then maintained inflated for approximately 1 min. A longer compression resulted in a profound hypoaesthesia that sometimes led to a complaint of dysaesthesias. As well as being found for other lesional surgical strategies, the more the sensorial deficit, the longer the pain-free interval but the higher the rate of severe dysaesthesia.

However, PMC is easy to perform, and the recurrence rate is acceptable with a low rate of complication even in the case of repeated surgery. Diplopia was sometimes observed but it was generally transient. This is our favourite method when MVD fails or is refused by the patient.

Radiosurgery

Stereotactic gamma knife radiosurgery was first reported for the treatment of TN by Leksell in 1971 [32]. Its use, however, remained restricted to a few centres until the mid-1990s when it started to become more widely used. Radiosurgical treatment of TN has been well investigated with gamma knife devices involving fixed cobalt sources. Few reports exist concerning TN treated using linear accelerator (LINAC)-based devices and only one study reporting on patients treated with CyberKnife is available in the literature [33]. In our Institution CyberKnife has been available since March 2004 but our data are too preliminary to be reported. Substantial advantages have been supposed in safety and comfort over other modalities but so far the evidence is based on case series with a single randomised study comparing two methods of delivery of radiotherapy [34]. Radiosurgery appears as a lesional procedure with a strong correlation between the development of new facial sensory loss and achievement and maintenance of pain relief [34]. Quality of data is generally poor: case series have different patient populations, varying doses of radiation and targets, a variety of assessment methods and differing follow-up. 70–80% of patients are pain-free in the short term, although up to 50% may relapse. Side effects include facial dysaesthesia (up to 12%), corneal irritation, vascular damage, hearing loss and facial weakness, varying with the dose plan and target area. Follow-up is generally short and uncertainty persists about possible late complications of radiation therapy.

Conclusions

MVD is the only surgical option that allows for obtaining long-term pain relief avoiding any sensory disturbance. In our opinion it remains the treatment of choice for all patients with drug-resistant typical TN. Old age and central demyelination do not constitute absolute contraindications to this kind of surgery. In addition, although the results of MVD in patients affected by MS (as well as the results of percutaneous methods) [26] are less satisfactory, about 40% of MS-TN patients were found completely pain-free at long-term follow-up. As sensorial deficits can be far from negligible and well tolerated in some patients treated with lesive procedures, our policy is to delay destructive surgery as much as possible. When these procedures cannot be avoided PMC should be first proposed because it is easy to perform with low general morbidity, especially on trigeminal sensitivity. In cases requiring more aggressive treatments because of recurrent pain TRZ can be employed. The use of radiosurgery is still under investigation and further studies are required to clarify its role in the treatment of TN. In MS patients, unfortunately both MVD and lesioning procedures cannot prevent pain recurrence due to MS-related evolving demyelination. Thus, new treatments aiming to modulate the activity of central trigeminal pathways should be investigated to improve the quality of life of these unfortunate patients, refractory to all available surgical and medical therapies. Chronic deep brain stimulation at the thalamic–hypothalamic level might be an interesting option that is at present under evaluation at our institution.

Surgery for atypical facial pain

The less the paroxysmal component of facial pain, the more contraindicated are all the surgical procedures that are able to produce any damage to the nervous system. Either PMC and TRZ as well as radiosurgery should be avoided in cases with atypical features because the risk of developing a neuropathic pain worse than the initial pain is very high. MVD can be employed by experienced groups in patients with mixed paroxysmal and constant pains, only when MRI clearly depicts a neurovascular compression of cranial nerves involved in the transmission of facial sensations. In cases without paroxysmal pain the classical neurosurgical armamentarium used for TN should not be considered. In these cases a new approach based on the capability of functional diagnostic studies (PET, SPECT, fMRI, etc) to identify the areas of the nervous system possibly involved in pain genesis should guide the neurosurgeon. In the modern neurosurgical armamentarium against pain there are, in fact, new weapons such as central and peripheral nervous system stimulation whose role is still to elucidate, but that are, however, very promising as shown by the recent studies in the field of cluster headache and other chronic facial pains [35–38]. Finally, the capability of neurosurgeons to interfere with chronic pain through the infusion of drugs directly within the CSF should not be forgotten.

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Facial pain in children and adolescents

Abstract Facial pain is a debilitating disorder if left untreated. It has been suggested that the most commonly undiagnosed facial pain conditions include neuropathic and myofascial pains because their pathophysiologies are not well understood. Facial neuralgias are otherwise rare in children. They are not acknowledged in most paediatric tests, there are few published reports on them, and glossopharyngeal neuralgia (GPN) has not been described in children. Some of the most common forms of facial pain will be considered and some considerations concerning the problem of atypical facial pain in young age and its treatment will be discussed.

Key words Typical and atypical facial pain • Children and adolescents • Pharmacological treatment • Surgical treatment

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Introduction

Facial pain is a debilitating disorder if left untreated. Too often patients are labelled as having psychopathology when face pain aetiology is unclear. In fact these patients are categorised as "atypical", "idiopathic" or "psychogenic". The term idiopathic suggests that there is something unknown and does not define the problem. The same applies to terms incorporating the word atypical [1].

It has been suggested that the most commonly undiagnosed facial pain conditions include neuropathic and myofascial pains because their pathophysiologies are not well understood and facial pain may be neurological vascular or dental in origin.

Dental pain is far more common than trigeminal neuralgia (TGN). Neurological and vascular causes of facial pain are rare compared with dental and temporomandibular causes [1]. Facial neuralgias are otherwise rare in children.

TGN, GPN, occipital neuralgia and Bell's palsy are neurological causes of facial pain in children, although they are very rare. They are not acknowledged in most paediatric tests, there are few published reports on them, and GPN has not been described in children. Both these conditions may be debilitating for children and they have to be considered in children presenting with paroxysmal facial, ear and throat pain. Also, cluster headache is a rare entity in childhood and few case reports have been demonstrated in the literature [2].

Many difficulties arise with the condition that used to be known as atypical facial pain (an inappropriate term, as many cases conform to a pattern). The fact that some cases follow surgery or injury to the face, teeth or gums suggests the possibility of an infectious or traumatic cause. These forms have been recently included in the new version of the IHS classification [3]; they have been located in section 13 of the IHS: 'Cranial neuralgias and central causes of facial pain'.

In particular, section 13.18.4 concerns 'Persistent idiopathic facial pain' (previously used term: atypical facial

pain), which does not have the characteristics of the cranial neuralgias and is not attributed to another disorder.

The IHS criteria for the diagnosis of headache in children have considered some particular aspects for young patients and it has been confirmed that the unilateral location of pain is not a specific feature of juvenile headache

The unilaterality of pain at a young age, especially in children, is not a common typical event of migraine forms. If headache is always present unilaterally before a diagnosis of migraine or tension-type headache is given, secondary forms or other forms of facial pain must be excluded. Anamnestic data, a careful neurological examination and instrumental examination are needed [4].

We will consider some forms of facial pain that can be noted in children, both typical and atypical, and some news about the most helpful treatments will be mentioned.

Trigeminal neuralgia

It is estimated that typical TGN occurs in about 1 in 25 000 of the population and is uncommon prior to the third decade, with 1% of cases occurring before the age of 20 years.

The appearance of TGN in infancy is exceptionally rare. There are few reports of TGN in the paediatric literature. Childs et al. [5] described 3 children who presented over a 2-year period with severe debilitating facial pain as a result of neurovascular compression of their cranial nerves [6].

Symptomatic TGN is a rare entity in childhood. It may be associated with multiple sclerosis and is sometimes the first manifestation of the disease. In cases of multiple sclerosis, TGN may be bilateral. Other cases are tumours and vascular malformations. TGN as the only manifestation of a Chiari type 1 malformation may occur, but infrequently. Ivanez described the case of a 39-year-old man who had presented with recurrent pain in the right maxillary region since 8 years of age [7]. The first clinical report of idiopathic trigeminal sensory neuropathy occurring in childhood was presented by Matoth et al. in 2001 [8].

Nevertheless, the age at which patients may be affected is controversial. Idiopathic TN occurs occasionally in childhood although in some rare cases successful microvascular decompression has been performed also at this age [9].

Glossopharyngeal neuralgia

Although GPN is a much rarer condition, based on numerous anecdotal reports it is believed that in the absence of a tumour the idiopathic form may also result from arterial compression of the nerve as it leaves the brain stem.

This condition can be debilitating and is extremely rare in children. It has been reported following amygdalectomy or tonsillectomy or in children with a Chiari 1 malformation [6]. The pain of GPN is intense and paroxysmal. It originates in the throat in the tonsillar fossa and is provoked most commonly by swallowing, but also by talking, chewing, yawning and laughing. Childs et al. [5] described a 13-year-old girl with GPN who presented with a history of paroxysmal pain in the right ear from infancy. MRI of her brain was normal but MRA revealed a prominent looping right posterior inferior cerebellar artery compressing the right 9/10 nerve complex at its exit from the medulla.

Occipital neuralgia

Paroxysmal pain occasionally occurs in the distribution of the greater or lesser occipital nerves. It is not uncommon in children with stenosis of the foramen magnum in achondroplasia. It has also been known to occur in traumatic injuries, especially in adolescents [6]. It has been reported in a 9-year-old patient with occipital neuralgia as a complication of varicella infection.

Bell's palsy

Bell's palsy is an acute idiopathic paralysis of the facial nerve. The first clinical manifestations may be pain or paraesthesias in the ear or the face ipsilateral to the facial palsy. Lacrimation is preserved in many cases but taste sensation is lost in about half the patients.

Complete recovery is the rule in children. Delayed or incomplete recovery may occur if there is marked denervation. Aberrant regeneration is exceptional in children [6]. The annual incidence is 3/100 000 in the first decade and 10/100 000 in the second decade. The treatment is symptomatic. It is essential to protect the cornea with lubricants and patching. Corticosteroid use is controversial in children because there is no proof of its efficacy.

Cluster headache

Differential diagnosis of facial pain cannot be performed without considering this important headache form. Cluster headache represents an occasional case of severe unilateral head pain.

Although it is rare in childhood, occasional cases have been reported in the literature [10, 11], showing a prevalence of 0.09%–0.4% for males, much less common than migraine.

Childhood onset cluster headaches resemble the adult form with regard to the site and type of pain, the predominance in males and the associated symptoms. The most

common symptom in childhood is lacrimation on the ipsilateral side and then conjunctival injection.

Cluster headache in paediatric patients is rarely recognised and children often suffer for years before receiving the correct diagnosis and treatment [12]. The proposed treatments are the same treatments used in adults.

Treatment of facial pain

There are few studies on the treatment of facial pain in children. Most studies are on adults and focus on TGN. In practice, children have been treated similar to adults. In adults, some success was obtained initially with phenytoin. Medical control became a possibility after introduction of carbamazepine, which is the most widely used and effective drug in treating TGN [13]. Other anticonvulsants such as divalproex sodium and lamotrigine may also be effective, though to a lesser extent [14].

Dosages of the antiepileptic drugs used to treat TGN are the same as those used to treat epilepsy; the dosages have to be modified according to body weight in children. The goal is a therapeutic blood level.

Tricyclic antidepressants such as amitriptyline and nortriptyline may also be used. The antiepileptic medications and tricyclic antidepressants can be combined in refractory patients. The dosages in children will be modified by considering the body weight.

Surgical treatment consisting of microvascular decompression is thought to be a safe and effective treatment in adults. Little data on children is available [7]. Two children with severe TGN described by Childs et al. [5] underwent a craniotomy for microvascular decompression. Neither of them responded quickly to the surgery and repeated procedures were necessary to achieve symptom control. Adults whose symptoms begin in childhood also do not have the same therapeutic response as patients with later onset symptoms [9].

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Migraine with aura from pathophysiology to treatment: therapeutic strategies

Abstract Migraine with aura (MwA) sufferers, at times, need specific treatments. This is the case when the auras are frequent, prolonged and cause anxiety and distress. Abnormal release of glutamate, that may trigger auras, and abnormal platelet behaviour, that constitute a possible predisposing factor to MwA, may be possible targets for MwA specific prophylactic therapy. Here we present results obtained by using lamotrigine, an agent known to inhibit glutamate release, and picotamide, an antiplatelet drug. Both drugs significantly reduced, in two open label trials, the frequency and the duration of auras. In comparison with lamotrigine, the therapy with picotamide may offer some advantages, such as the use of the therapeutical dose from the first day of treatment (lamotrigine needs one month to reach such a dose) and the possibility to prevent cerebral ischaemic events and migraine stroke, a rare but severe complication of MwA attacks.

Key words Lamotrigine • Migraine with aura • Neuronal hyperexcitability • Picotamide • Platelet activation

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Introduction

Migraine with aura (MwA) is a primary headache disorder that affects about 30% of migraine sufferers [1]. In some patients, MwA is associated with attacks of migraine without aura: coexistence in individuals has sparked a debate as to whether these two forms of migraine are actually two clinically distinct entities. The International Headache Society's (IHS) diagnostic criteria for MwA [2] provide a clinical description of the aura, the disorder's most distinctive feature: aura consists of transient, unilateral or bilateral visual, sensory or motor symptoms considered to arise from a recurrent reversible, idiopathic dysfunction of the cortex or brainstem.

The most challenging task for the physician confronted with this easy-to-diagnose form of migraine is to select the most effective treatment course. A thorough history is important to uncover possible trigger factors such as oral contraceptives and light stimuli. Once these have been identified, the main questions are what drugs to use and whether a preventive regimen is justified. A no less important consideration is whether the aura should be specifically treated. This is particularly relevant when the duration of neurological symptoms and the modality of their appearance may constitute a cause of a severe anxiety and distress in these patients (sudden loss of vision in visual field, strength in one arm, etc). This occurs more often when the aura lasts one hour or more (at times the symptoms of aura last days as in prolonged auras) and the frequency is high. In addition, although very infrequent, aura

may trigger a cerebral ischaemic attack with permanent neurological deficits (migraine stroke). The review of the literature search (databases used were MEDLINE on PubMed, Embase, Healthstar, Cochrane databases and CINAHL) on the acute treatment of the aura and its prophylaxis indicates that the therapeutic options to cope with needs of MwA sufferers are very few and not always tailored to prevent the neurological symptoms [3].

Here we briefly describe the possible chain of events of aura pathophysiology and circulating factors that could predispose and/or precipitate MwA attacks. Based on this evidences, we suggest MwA possible specific therapeutic strategies.

Aura pathophysiology

Functional evidence suggests that the visual aura is a neuronal event similar to the spreading depression (SD) triggered on the cortex of the rabbit by potassium described by Leao [4]. The initial event is a spontaneous neuronal depolarisation moving slowly (3 mm/min) on the occipital cortex, which has the clinical counterpart in the scintillating contour (positive scotoma). The negative scotoma (the dark area inside scintillations) may represent the following suppression of neuronal function [5]. Neurophysiological studies, using neuromagnetometer and transcranial stimulation of occipital cortex, support the hypothesis that neuronal hyperexcitability [6] is the predisposing factor that causes the initial cortical event [7, 8]. Glutamic and aspartic acids are excitatory amino acids that elicit and support SD in animal models [9]. Elevated levels of these excitatory neurotransmitters have been found in platelets of MwA sufferers [10, 11]. Platelets constitute a fair model to study glutamate function of the neuron [12]. Thus, if these platelet findings mirror the similar abnormal levels in neurons, it is possible that an increased release of glutamate from dendrites or soma depolarises occipital cortex mediating SD.

The factors that predispose to MwA attacks are unknown, however an increased susceptibility to platelet dense bodies (in which glutamate is contained) release [13–15] together with a low threshold of platelet to aggregating agents such as platelet activating factor (PAF) and ADP may predispose to auras in MwA sufferers [16–18]. This is a possible pathological occurrence when platelet anomalies match with the presence of patent foramen ovale (PFO) [19] and atrial septum aneurysm (ASA) [20], heart conditions significantly more frequent in MwA. The abnormal platelet behaviour that characterises MwA patients, together with heart congenital anomalies, increases the possibility of platelet aggregate formation in the microcirculation with local release of glutamate and possible focal minute cerebral ischaemia. Both events may determine release of potassium and glutamate from glia and cortical neurons in MwA, in which a defect of brain oxidative metabolism has been demonstrated [21], and auras.

From pathophysiology to treatments of MwA

Release of glutamate from platelet and neurons may constitute an important step in triggering neuronal depolarisation and the occurrence of auras. Hence drugs that potentially interfere with the impact of glutamate on hyperexcitable neurons may prevent MwA attacks.

Lamotrigine is an antiepileptic agent active in blocking partial seizures and generalised as well [22]. It acts by blocking voltage-dependent sensitive channels, leading to inhibition of neuronal release of glutamate [23]. We have treated, in an open label study, 24 MwA patients with high frequency of attacks (6.1±4.1), during a one month run reported in a diary, with 100 mg of lamotrigine on a daily basis (starting with 25 mg day and increasing by 25 mg every week). The frequency of attacks decreased significantly from 6.1±4.1 to 0.7±1.3/month ($p<0.0001$) during a three-month trial. The duration and the intensity of the pain of residual crisis remained unchanged. Five patients suffered also from migraine without aura attacks, the frequency of which was not modified by treatment [24]. The latter finding confirms that lamotrigine is not useful in migraine without aura, where the cortical events triggered by glutamate are not present [25]. The usefulness of lamotrigine is confirmed by other open label studies [26–29], suggesting that it can constitute a possible specific prophylactic treatment of MwA.

Another possible option for MwA prophylactic treatment is to reduce the low threshold to platelet activation and aggregation in MwA patients. This therapeutic strategy may be particularly useful in those subjects with a concomitant presence of PFO and ASA, where the possibility of platelet microaggregates occurrence is more probable. Picotamide is an antiplatelet agent with a dual mechanism of action: inhibition of thromboxane A_2 synthase and antagonism of TX_2 receptors [30]. In order to ascertain the possible usefulness of picotamide, we performed a pilot study administering the drug, at the dose of 300 mg twice daily, to 22 patients affected by MwA with high frequency of attacks (6.85±3.83 in the run-in trimester). A detailed diary reporting neurological symptoms, duration of the aura and frequency of attacks was compiled by patients along the trial time (6 months of picotamide regimen). Picotamide has shown a significant efficacy in reducing the number of auras (from 6.85±3.83 to 2.55±2.89/month; $p<0.0001$) and their duration (from 36.75±20.28 to 17.75±16.26 min; $p<0.0001$). In 25% of patients MwA totally disappeared. No serious adverse event accompanied the treatment. The results demonstrate that picotamide is a useful therapy in the prophylaxis of MwA [31].

Conclusions

The results obtained from our studies clearly suggest that it is possible to prevent MwA attacks with agents that interfere with the pathophysiological chain of events that may trigger the aura. Lamotrigine, in contrast to topiramate [32], another antiglutamatergic drug known to be highly effective in the therapy of epilepsy, seems to be a specific treatment. Promising results are obtained by using an antiplatelet agent such as picotamide. Like lamotrigine, picotamide significantly reduces the frequency and length of auras. This treatment is particularly indicated when platelet activation is more probable to occur, i.e., in those patients with PFO and/or AsA. One advantage of picotamide *vs*. lamotrigine is that using the former the therapeutic dose of the drug can be administered early, from the first day of treatment. Lamotrigine has to be increased slowly and needs one month to reach the proper dose. In addition, picotamide treatment is a good prophylaxis to prevent ischaemic events [33] and migraine stroke, which is an infrequent but severe complication of MwA attacks [34].

Indeed, the results obtained with lamotrigine and picotamide have to be confirmed with double blind, placebo-controlled trials.

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Early triptan intervention in migraine: an overview

Abstract Although triptans are highly effective for the acute treatment of migraine, sustained pain-free rates – considered the optimal end-point – are in the range of 18%–27% for all triptans in clinical trials. A recently proposed strategy for treating migraine attacks is that triptans should be given early, when the pain is mild, rather than moderate or severe. Studies with different triptans have shown that early intervention can result in higher pain-free rates, together with reductions in rescue medication use and recurrence rates. However these studies suffer from methodological pitfalls: most were retrospective analyses of trials not designed to evaluate the benefit of early intervention; the definition of "early" differed from study to study; and placebo effects were not correctly evaluated. Furthermore, the disadvantages of this strategy in clinical practice, particularly the risk of medication overuse, have not been evaluated. We propose that only patients with particularly severe migraines and in whom attacks are always characterised by rapid progression of pain and other symptoms, should be advised to take a triptan as early as possible.

Key words Triptans • Migraine • Early intervention

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Introduction

Migraine is a chronic intermittent disorder with high prevalence in western countries, characterised by moderate to severe pain and associated with considerable functional disability [1]. The introduction of 5HT 1B/1D agonists, known as triptans, over a decade ago began a new era in migraine therapy [2]. Despite the improved effectiveness of triptans, they are not effective in all patients, and many sufferers are not satisfied with the acute treatments available to them. The optimal way of managing migraine attacks cannot be considered to have been elucidated [2–5]. In recent years, the early intervention strategy, by many thought to enhance the effectiveness of anti-migraine therapy, has received considerable attention.

Efficacy of triptans in clinical trials

In most triptan trials, patients were instructed to take the study medication when the pain was moderate-severe, as the primary end-point was the proportion of patients achieving headache response (or relief), defined as change from pain level 2 (moderate) or 3 (severe) to level 0 (no pain) or 1 (mild) two hours after dosing [2, 3]. However, it has been found that patients expect to obtain rapid and total relief from pain and accompanying symptoms with low recurrence rate, and that many migraine patients are unsatisfied with the treatment according to these criteria [4, 5]. This led the International Headache Society (IHS) to propose sustained pain-free response (pain-free state within 2 h after dosing, with no use of rescue medication and no recurrence of headache within 24 h) as the optimal end-point [6]. This end-point seems difficult to achieve: a recent meta-analysis of trials with oral triptans showed that in only 18%–27% of cases were sustained pain-free states obtained [7].

Evidence in favour of early intervention

That triptan efficacy may be enhanced by treating the migraine attack when the pain is mild was first suggested by Cady et al. [8], based on the post hoc analysis of a subgroup of 26 patients enrolled in the Spectrum Study (a randomised, double-blind, placebo-controlled, crossover study in which sumatriptan 50 mg was tested against placebo). The 26 patients were protocol violators who treated 46 mild and 166 moderate-severe headaches with sumatriptan or placebo. Pain-free rates at 2 and at 4 h were significantly higher when attacks were treated when pain was mild (at 2 h: 50% with sumatriptan and 0% with placebo; at 4 h: 85% and 19%, respectively) compared with pain-free at 2 and 4 h for attacks treated after pain had progressed to moderate or severe (at 2 h: 27% with sumatriptan and 6% with placebo; 4 h: 48% and 19%, respectively). Furthermore, the recurrence rate was lower for mild attacks than for moderate or severe attacks. Cady et al. concluded that patients with disabling migraine may benefit from early intervention.

Retrospective studies have been published concluding that early treatment with almotriptan is effective [9–12]. In the study of Dowson et al. [11], early intervention (defined as drug administration within an hour of onset of moderate or severe pain) with almotriptan, 12.5 mg, was found associated with pain-free rates that were similar to or higher than those obtained with sumatriptan 100 mg, and significantly higher than placebo.

More recently, three prospective studies using different triptans have been conducted [13–15]. Rizatriptan assumption immediately after experiencing headache was associated with more rapid headache relief (odds ratio 1.33), more frequent symptom-free state, and more frequent return to normal activities within an hour post-dose (odds ratio 1.34) than taking the drug when the headache was moderate-severe [13]. Klapper et al. [14] prospectively treated patients, who typically experienced mild pain initially that progressed to moderate or severe pain, with zolmitriptan 2.5 mg. They found significantly better outcomes than with placebo. They also found that zolmitriptan was effective in patients treating during the first 15 min of pain onset.

Scholpp et al. [15] performed a prospective, randomised study, comparing headache sumatriptan 100 mg assumption within an hour of headache onset *versus* when the pain was moderate-severe. At two hours post-dose 71.1% of early intervention patients and 54.5% of delayed intervention patients were pain-free: the difference was just significant (p=0.043, Fisher's exact test).

Pathophysiological basis of early intervention

Migraine is progressive within an attack. Initial peripheral activation and sensitisation affecting the meninges and blood vessels leads to throbbing pain; later, additional central sensitisation of the trigeminal nucleus caudalis occurs, and cutaneous allodynia develops [16, 17]. Burstein and colleagues suggested that the presence of cutaneous allodynia may influence the response to triptans [18] as they found that sumatriptan administration before allodynia onset led to complete headache relief, while in attacks treated after cutaneous allodynia was already established sumatriptan was less effective, and was not able to suppress the ongoing allodynia. Hence, early treatment seems to reduce or even prevent central sensitisation, and as allodynia develops during the first hour of an attack in most migraine patients, this period would constitute the limited window of opportunity for achieving optimal therapeutic response [19].

Critique

As discussed by M. Ferrari in an editorial [20], most of the evidence for the efficacy of early triptan intervention in migraine is derived from retrospective analyses of data from trials not designed to evaluate the benefit of early intervention. A second weakness is that in all cases, patients with slowly progressing attacks were not distinguished from those with rapidly progressing attacks. This problem may be also present in studies comparing early *vs*. delayed intervention in the same patients, as progression may differ across attacks in a single patient.

With regard to the few retrospective trials that have been published, there are difficulties with generalising the results because of the defects in study design. Klapper et al. [14] compared early intervention with zolmitriptan *vs*. early intervention with placebo in two randomised populations – but without direct comparison with delayed intervention, either with active drug or with placebo. In the other two studies, the outcomes obtained with early intervention with rizatriptan [13] or sumatriptan [15] were compared to those obtained with delayed intervention with the same drugs in the same population, but the results were not placebo-controlled. It is also important to note that the meaning of "early" intervention was not constant: the term may refer to drug administration "as soon as the migraine begins" or "when the pain is still mild", and these are not the same thing.

Another aspect to consider is that early intervention may have disadvantages in clinical practice. Firstly patients may be tempted to use triptans to treat short, self-limiting migraine or tension-type headache attacks. Secondly by proposing that each and every headache should be treated as soon as possible, there is a danger of inadvertently encouraging medication overuse, particularly in patients with frequent migraines.

To conclude, treating migraine attacks when the pain is mild may lead to better headache control and greater reduc-

tion of disabling consequences, at least in some patients. However, the real effectiveness of early triptan administration has not been established by properly designed prospective trials, while encouraging patients to "reach for the triptans" the moment they feel a headache starting may enhance the risk of medication overuse. We advise caution: only patients with particularly disabling migraines, who have a high recurrence rate, or in whom attacks are always characterised by rapid progression of pain with triptans and of symptoms should be encouraged to treat their attacks as quickly as possible.

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KEY NOTE LECTURE

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Migraine preventive therapy: current and emerging treatment options

Abstract In this paper we review new treatment options for migraine prevention. We start with an overview about migraine and then briefly discuss current indications for migraine prevention and new and emerging preventive medications.

Key words Migraine prevention • Migraine prophylaxis • Migraine treatment

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Introduction

Migraine is a chronic neurological disease characterised by episodic attacks of headache and associated symptoms. In Western countries, the condition affects 11% of the adult population [1]. Migraine is a heterogeneous condition that results in a range of symptom profiles and various degrees of disability both within and among different individuals [2]. The disability caused by migraine can be severe and imposes a considerable burden on the sufferer and society [3–5]. In this paper we review new treatment options for migraine prevention. We start with an overview about migraine pathophysiology and then briefly discuss current indications for migraine prevention and new and upcoming preventive medications. Because we focus on new medications, some of the data we present herein were acquired in well designed double-blind, controlled studies, while the efficacy of other drugs is supported only by open, uncontrolled trials (noted in the text wherever appropriate).

Principles of migraine prevention

Migraine pharmacotherapy is usually divided into two categories: drugs that are taken daily whether or not headache is present to reduce the frequency, duration and severity of attacks (preventive therapy) and drugs that are taken acutely to stop attacks (acute care therapy) [6, 7]. The US Headache Consortium Guidelines [8, 9] suggest that preventive treatment should be considered in the following circumstances:

- recurring migraine that significantly interferes with the patient's daily routine despite acute treatment (e.g., two or more attacks a month that produce disability that

lasts ≥3 days, or headache attacks that are infrequent but produce profound disability);
- failure of, contraindication to, or troublesome side effects from acute medications;
- overuse of acute medications;
- special circumstances, such as hemiplegic or basilar migraine or attacks with a risk of permanent neurological injury;
- very frequent headaches (more than two a week), or a pattern of increasing attacks over time, with the risk of developing rebound headache with acute attack medicines;
- patient preference, i.e., the desire to have as few acute attacks as possible.

It is not clear how preventive therapy works, although it seem likely that it modifies the sensitivity of the brain that underlies migraine [10].

Medications from a broad range of classes have demonstrated efficacy in preventing migraine. Clinicians are most familiar with the data supporting use of β-adrenergic blockers, antidepressants, calcium-channel antagonists and valproate [10]. Some of these effective agents were discovered serendipitously after use for other purposes and still represent the majority of prescriptions written for migraine prevention. Because most of them are considered standard preventive medications, they will not be discussed.

Some of the available options are listed in Table 1, and the evidence regarding their use has been extensively reviewed (Table 2) [9]. When deciding to initiate preventive pharmacotherapy, several general principles of management may prove helpful:

Begin the preventive medications at a low dose and gradually increase the dose over weeks or months if necessary. For example, if no side effects emerge and if the desired clinical response has not yet been achieved, and the ceiling dose for the drug has not been reached, the dose can be escalated.

Manage the patient's expectations regarding the time and extent of clinical benefit. Many preventive medications take a minimum of 3 or 4 weeks for a therapeutic response at a particular dose; patients need to be patient and compliant with the agreed-upon treatment plan. Two thirds of the patients given any of the drugs listed in Table 3 will have a 50% reduction in the frequency of headaches. Breakthrough headaches are inevitable and must be managed with acute treatment. It is important to explain the side effects of these drugs and engage the patient in the decision-making process.

Establish a comprehensive migraine management plan that includes long-term goals, tips on when the medication needs to be changed, a regular office visit schedule and specific information on adverse reactions that may warrant discontinuing the medication, returning to the clinic, calling the office or even going to the hospital on an emergency basis.

Table 1 Selected preventive therapies for migraine

Generic treatment	Doses
Alpha2-agonists	
Clonidine tablets	0.05–0.3 mg/day
Guanfacine tablets	1 mg
Anticonvulsants	
Divalproex sodium tablets*	500–1500 mg/day
Gabapentin tablets*	300–3000 mg
Levetiracetam tablets	1500–3000 mg
Topiramate tablets*	50–400 mg
Zonisamide capsules	100–400 mg
Antidepressants	
MAOIs	
Phenelzine tablets	30–90 mg/day
TCA	
Amitriptyline tablets*	30–150 mg
Nortriptyline tablets	30–100 mg
SSRIs	
Fluoxetine tablets	10–40 mg
Sertraline tablets	25–100 mg
Paroxetine tablets	10–30 mg
Venlafaxine tablets	37.5–225 mg
Mirtazapine tablets	15–45 mg
Beta-blockers	
Atenolol tablets*	25–100 mg
Metoprolol tablets	50–200 mg
Nadolol tablets	20–200 mg
Propranolol tablets*	30–240 mg
Timolol tablets*	10–30 mg
Calcium channel antagonists	
Verapamil tablets*	120–480 mg
Nimodipine tablets	30 mg tid
Diltiazem tablets	30–60 mg tid
Nisoldipine tablets	10–40 mg qd
Amlodipine tablets	2.5–10 mg qd
NSAIDs for prevention	
Naproxen sodium tablets*	500–1100 mg/day
Ketoprofen tablets	150 mg/day
Mefanamic acid tablets	1500 mg/day
Flurbiprofen tablets	200 mg/day
Anti-serotonergic agents	
Methysergide tablets*	2–12 mg
Cyproheptadine tablets	2–16 mg
Pizotifen tablets*	1.5–3 mg
Miscellaneous	
Monteleukast sodium tablets	5–20 mg
Lisinopril tablets	10–40 mg
Candesartan	8–32 mg/day
Botulinum toxin A injection	25–100 units (IM)
Feverfew tablets	50–82 mg/day
Magnesium gluconate tablets	400–600 mg/day
Riboflavin tablets	400 mg/day
Petasites 75 mg*	75 mg bid
Coenzyme Q10	300 mg/day

*Evidence for moderate efficacy from at least two well designed placebo-controlled trials

Table 2 Choices of preventive treatment in migraine

Drug	Efficacy	Adverse events	Comorbid condition	
			Relative contraindication	Relative indication
Beta-blockers	4+	2+	Asthma, depression, congestive heart failure, Raynaud's disease, diabetes	Hypertension, angina
Antiserotonin				
Pizotifen	4+	2+	Obesity	
Methysergide	4+	4+	Angina, vascular disease	Orthostatic hypotension
Ca channel blockers				
Verapamil	2+	1+	Constipation, hypotension	Aura, hypertension, angina, asthma
Flunarizine	4+	2+	Parkinson's, depression	Dizziness, vertigo
Antidepressants				
TCAs	4+	2+	Mania, urinal retention, heart block	Depression, anxiety, insomnia, pain
SSRIs	2+	1+	Mania	Depression, OCD
MAOIs	4+	4+	Unreliable patient	Refractory depression
Anticonvulsants				
Divalproex/valproate	4+	2+	Liver disease, bleeding disorders	Mania, epilepsy, anxiety
Gabapentin	2+	2+	Liver disease, bleeding disorders	Mania, epilepsy, anxiety
Topiramate	4+	2+	Kidney stones	Mania, epilepsy, anxiety
NSAIDs	2+	2+	Ulcer disease, gastritis	Arthritis, other pain disorders

*Ratings are on a scale from 1+ (lowest) to 4+ (highest) based on strength of evidence. From reference [34], with permission

Table 3 Efficacy of levetiracetam in the preventive treatment of refractory transformed migraine

Endpoint	Baseline	3 months	*p* value
Headache frequency	24.9	18.0	<0.001
Moderate or severe headache	16.8	11.7	<0.01
MIDAS scores	62.8	40.8	=0.01
HIT scores	63.4	59.4	<0.01

Evidence regarding the preventive drugs is most available for the beta-blockers, antidepressants, calcium channel antagonists and anti-epileptic agents. We will briefly discuss these classes of drugs below.

Beta-blockers

The AHCPR Technical Report analysed 74 controlled trials of beta-blockers for migraine prevention [9]. Propranolol, nadolol, atenolol, metoprolol and timolol have been shown to be effective. The beta-blockers that are partial agonists and have intrinsic sympathomimetic activity have not been found to be effective for the prevention of migraine. As the relative efficacy of the different beta-blockers has not been clearly established, choice should be made based on beta-selectivity, convenience of drug formulation, adverse events (AEs) and the patient's individual reaction to a specific drug. Because beta-blockers can produce behavioural side effects such as drowsiness, fatigue, lethargy, sleep disorders, nightmares, depression, memory disturbance and hallucinations, they are best avoided in patients with depression. Decreased exercise tolerance limits their use by athletes. Less common side effects include impotence, orthostatic hypotension, significant bradycardia and aggravation of intrinsic muscle disease. Beta-blockers are especially useful for patients with comorbid angina or hypertension. They are relatively contraindicated for patients with congestive heart failure, asthma, Raynaud's disease and insulin-dependent diabetes.

Antidepressants

The currently available antidepressants consist of a number of different classes of drugs with different mechanisms of action. The tricyclic antidepressants (TCAs) most commonly used for migraine prevention include amitriptyline, nortriptyline, doxepin and protriptyline. Amitriptyline is the only antidepressant with fairly consistent support for its efficacy in migraine prevention. Other agents have not been rigorously evaluated; their use is based largely on clinical experience and uncontrolled reports [9]. Many headache experts use nortriptyline in preference to amitriptyline because of its more favourable AE profile. TCAs are better used for patients who have sleep disturbance or comorbid depression. Serotonin specific reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine and sertraline, can be used to treat coexistent depression, based on their favourable side-effect profiles; their efficacy as migraine preventives has not been established and they may increase migraine. Side effects from TCAs are common. Most involve anti-muscarinic effects, such as dry mouth and sedation. The drugs also cause increased appetite and weight gain; cardiac toxicity and orthostatic hypotension occur occasionally. Other classes of antidepressants such as serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine, as well as the miscellaneous ones such as bupriprion, have not been well studied.

Calcium-channel blockers

The AHCPR Technical Report identified 45 controlled trials of calcium antagonists [9]. A meta-analysis supports the clinical benefits of flunarazine (not available in the USA). Nimodipine had mixed results in placebo-controlled trials. The evidence for nifedipine was difficult to interpret. We avoid it as it is a significant vasodilator and may worsen migraine attacks. Verapamil was more effective than placebo in two of three trials, but both positive trials had high dropout rates. Of the calcium-channel blockers available in the USA, verapamil is the most widely used. Verapamil is especially useful for patients with comorbid hypertension or with contraindications to beta-blockers, such as asthma and Raynaud's disease. Calcium-channel blockers are also useful for patients who have migraine with prolonged aura or hemiplegia. Constipation and oedema are verapamil's most common AEs.

Antiepileptic drugs

Antiepileptic drugs (AEDs) are increasingly recommended for migraine prevention because of placebo-controlled, double-blind trials that prove them effective [9, 12–17]. Valproate or divalproex, topiramate and gabapentin have demonstrated efficacy [18].

Many patients find divalproex sodium to be effective at a low dose (500–1000 mg/day). Side effects include sedation, hair loss, tremor and changes in cognitive performance. Nausea, vomiting and indigestion can occur, but these are self-limited side effects. Hepatotoxicity is the most serious side effect, but irreversible hepatic dysfunction is extremely rare in adults. Pancreatitis has also been reported. Baseline liver function studies should be obtained, but routine follow-up studies are probably not routinely needed in adults on monotherapy. Young females seem to develop ovarian dysfunction at a higher rate than those on other AEDs. Patient follow-up is necessary to adjust the dose and monitor side effects.

Gabapentin (1800–2400 mg) was found to be superior to placebo in reducing the frequency of migraine attacks in a controlled, double-blind trial, supporting the results of previous open-trials. The responder rate was 36% for gabapentin and 14% for placebo [19]. The most common AEs were dizziness and drowsiness. Relatively high patient withdrawal rates due to AEs were reported in some trials.

Topiramate is a structurally unique anticonvulsant with rapid and almost complete oral absorption. Topiramate is either weight neutral or has been associated with weight loss, not weight gain (a common reason to discontinue preventive medication) with chronic use. Topiramate should be started at a dose of 15–25 mg/day at bedtime and increased weekly to 100–200 mg/day in divided doses. AEs include weight loss, paraesthesias and cognitive dysfunction (which is often prevented by slow gradual dose escalation). Topiramate should be used with caution in patients who have a history of renal calculi. A recent double-blind controlled study showed that topiramate is superior to placebo in the preventive treatment of migraine, supporting several previous open-label trials [20].

AEDs are especially useful when migraine occurs in patients with comorbid epilepsy, anxiety disorder or bipolar illness. They can be safely administered to patients with depression, Raynaud's disease, asthma and diabetes, circumventing the contraindications to beta-blockers. With the exception of valproic acid, many AEDs may interfere with the efficacy of oral contraceptives. Caution is therefore advised in women on AEDs and oral contraceptives. Topiramate occasionally causes breakthrough bleeding.

New options in migraine prevention

Levetiracetam

Levetiracetam (LTC) is a new anticonvulsant with an unknown mechanism of action. Its efficacy in migraine prevention may be related to a possible effect on cortical

spreading depression (CSD), which is an early pathophysiological process in a migrainous attack.

Open trials have shown the efficacy of LTC in the treatment of refractory migraine [21]. In an open study, Drake et al. [22] studied 10 patients with migraine with aura, 40 with migraine without aura and 12 patients suffering from daily headache. Other preventive and abortive medications were continued. There was a statistically significant decrease in headache frequency and severity after the first month.

A recent study performed at The New England Center for Headache in Stamford, CT, USA assessed the efficacy of LTC in the preventive treatment of refractory transformed migraine. Baseline data was collected from 35 subjects. Our ITT population consisted of 30 subjects (73.3% females, mean age of 46.5 years). A total of 9 (30%) subjects were not using other preventive drugs when included, 6 (20%) were using one preventive drug and 15 (50%) were using two or three preventive drugs. Median headache frequency per month at baseline was 24.9 (4.6) and a significant reduction of headache frequency was obtained in 1 month (19.4, $p<0.001$), 2 months (18.4, $p<0.001$) and 3 months (18.0, $p<0.001$) (Table 2). At baseline, the mean number of moderate or severe days was 16.8, compared to 13.2 after 1 month (NS). Significance was reached after 2 months (11.9, $p<0.01$) and 3 months (11.7, $p<0.01$). The mean MIDAS scores were significantly reduced at 3 months, compared to baseline (40.8 *vs*. 62.8, $p=0.01$). Mean HIT scores at baseline were 63.4, compared to 59.4 after 3 months ($p<0.01$). Fifteen (50%) patients reported side effects and, considering the ITT population, 5 (16.7%) dropped out of the study because of side effects. No serious AEs were reported [23].

LTC can be started at 250 mg at night and increased by 250 mg each week. Some physicians start at 500 mg hs and move up by 500 mg each week. Minimally effective doses appear to be 1500 mg and most patients need 2000–2500 mg/day with few AEs.

The side effects of LTC reported in initial clinical trials for epilepsy occurred in at least 3% of the patients and presented as fatigue or tiredness, somnolence, dizziness and infection (common cold or upper respiratory tract infection).

Zonisamide

Zonisamide (ZNS) is a sulphonamide derivative, chemically and structurally unrelated to other anti-epileptic drugs, recently introduced into the USA. It has been available in Japan and in Korea for over 10 years where it was usually indicated as an adjunctive therapy for partial seizures. Two open studies of ZNS in the treatment of refractory migraine were recently presented as abstracts showing its efficacy, especially regarding headache intensity and frequency [10, 24]. The first trial included 34 migraine patients who were resistant to other preventive treatments. ZNS was started in a dose of 100 mg/day and titrated, as tolerated, to 400 mg/day. The headache severity was significantly reduced but figures were not presented [24]. In the second study, 37 patients with refractory migraine and mixed headache syndromes were investigated. All had failed to respond to at least two preventive, but not specified, agents before. When the poster was presented 27 patients had already been evaluated and 14 patients revealed decreasing headache frequency [10]. Considering the fact that these studies involved very difficult to treat headache patients, these data support the potential utility of ZNS in the treatment of refractory migraine overall, although controlled studies are still lacking. The side effects reported in these studies were paraesthesias, fatigue, anxiety and weight loss. Agitated dysphoria and difficulty concentrating were also observed.

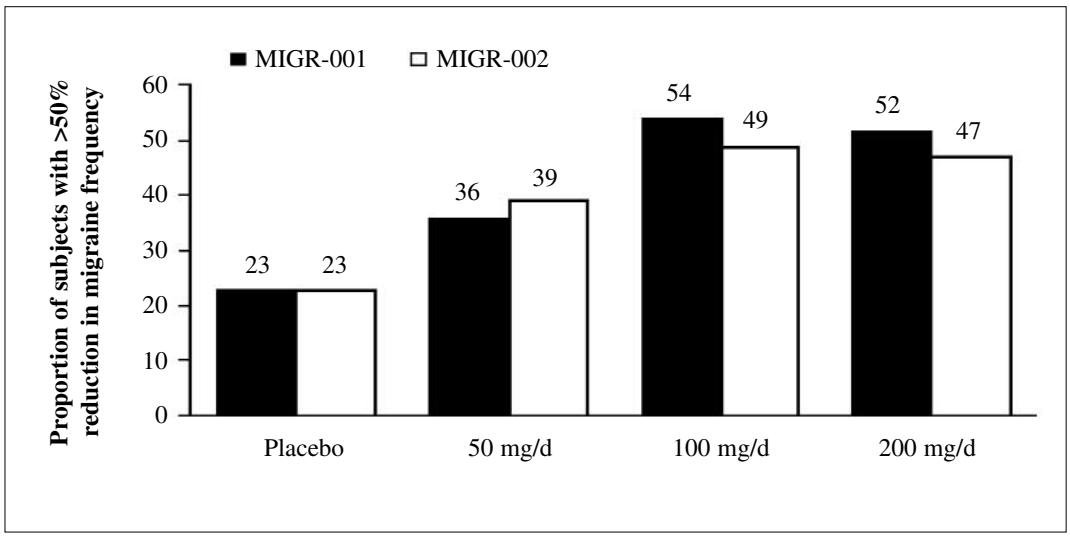

Fig. 1 Efficacy of topiramate in the preventive treatment of migraine (from reference [31], modified)

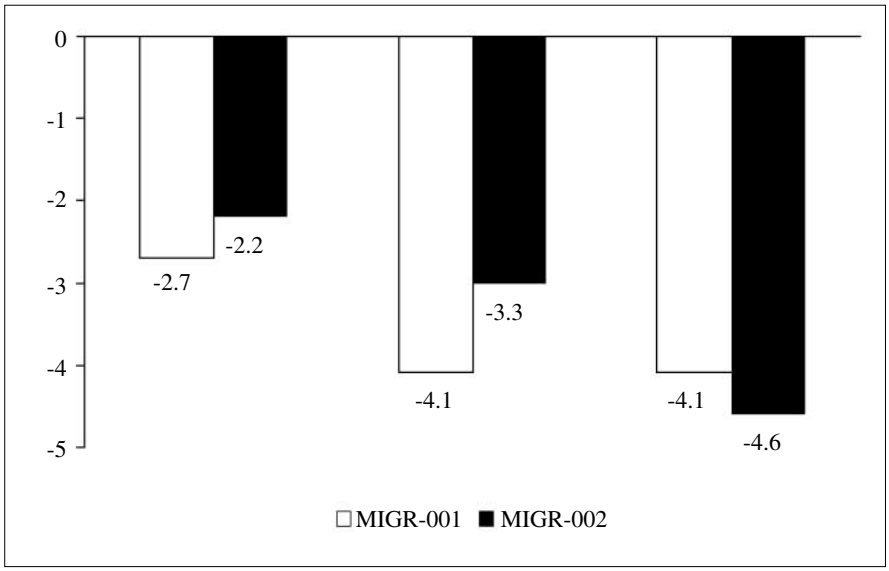

Fig. 2 Weight loss in participants of two clinical trials of topiramate in the prevention of migraine

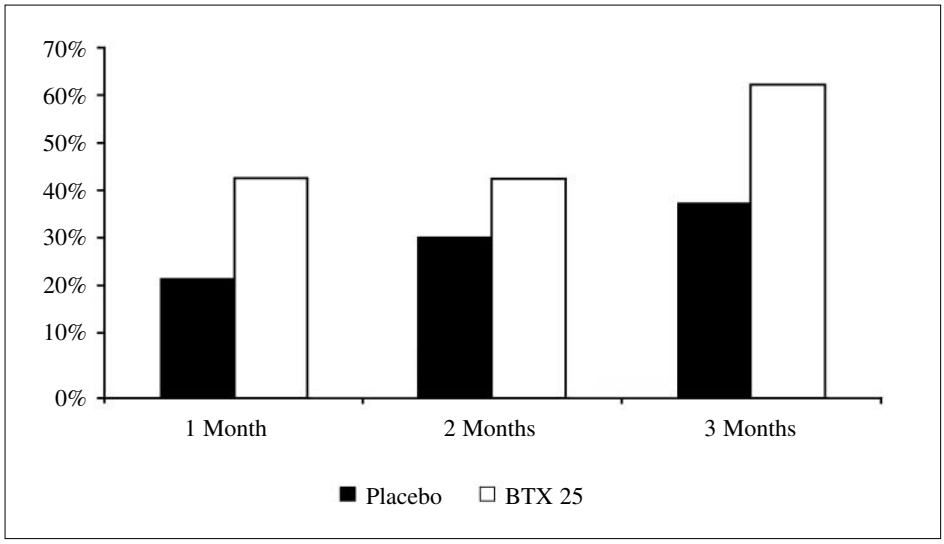

Fig. 3 Percentage of subjects with at least a decrease of two headaches in the frequency of their migraines (after reference [42]). $p<0.05$ at 3 months

Botulinum toxin (BTX)

BTX type-A injections often reduce the pain associated with conditions such as cervical dystonia, achalasia, rectal fissures and myofascial pain syndrome. BTX-A has been approved in the USA for blepharospasm and recently for forehead wrinkles. Some open-label, non-controlled studies of BTX-A suggested benefits for patients with migraine and tension-type headache [25–27].

BTX is a potent toxin that causes muscle paralysis when found pathologically. However, current migraine pathophysiological theories do not consider muscular factors as prominent. Recently, antinociceptive effects of BTX have been postulated. A study using rat trigeminal ganglion neurons demonstrated that BTX type A can directly decrease the amount of calcitonin gene-related peptide (CGRP) released from trigeminal neurons. The authors suggest that the efficacy of BTX-A may be at least partially explained by this mechanism as well as its direct effect on muscles [28]. Other studies have shown its effect in decreasing peripheral production of glutamate and substance P.

A recent double-blind study, evaluating 25 Units (25-U) and 75-U doses showed that, compared with vehicle treatment, subjects in the 25-U BTX type-A treatment group had significantly fewer migraine attacks per month, a reduced maximum severity of migraine pain, a reduced number of days using acute care migraine medications and reduced incidence of migraine-associated vomiting (Fig. 3). Those in the 75-U group were not significantly better than placebo [29].

A study assessing the efficacy of BTX-A in 100 patients with refractory headaches (migraine and chronic daily headaches) showed a statistically significant reduction of the frequency of headache days 1 month after BTX-A was administered (28.2 days *vs*. 14.2 days at the baseline, $p<0.001$), which was maintained through the three months of study; similarly, a significant reduction in the headache index (40.3 *vs*. 22.3, $p<0.001$) and number of severe days with headache per month (74.9 *vs*. 2.6,

$p<0.001$) were found at 1 month and maintained through the 3 months of study. MIDAS scores were reduced from 34.5 at baseline to 15.9 at 3 months ($p<0.001$) [30].

A typical treatment protocol is to inject BTX symmetrically into glabellar, frontalis and temporalis muscles and, if pain is present, also into pericranial and paracervical regions. The major side effect, avoidable with proper placement, is mild ptosis that usually lasts less than one week. Injections can be repeated every 3–4 months if patients have a beneficial effect, which wears off after 3–4 months post-treatment. Standard protocols tend to use 60–100 U in multiple sites from the forehead to the cervical muscles and note that patients often need repeat treatment in 3–4 months [31]. Some clinicians use higher doses. Side effects are usually mild and transient and include frontal weakness, ptosis (in migraine trials other kinds of weakness are infrequently reported) and pain in the sites of injections.

Tizanidine

Tizanidine (TZN) is a centrally acting, pre-synaptic alpha-2 adrenergic agonist only recently studied for use in headache patients. Its mechanism of action is thought to be through a decrease of norepinephrine release from the locus coeruleus in the upper, dorsal pons of the brainstem [32]. In a pilot open-label study, TZN was administered to 39 patients with more than 15 headache days per month. Thirty-one patients completed 12 weeks of treatment with an average of 14 mg/day (divided over three daily dosages). The overall headache index (frequency x average intensity x duration) declined significantly ($p<0.00000002$). Mild-to-moderate AEs, such as somnolence, asthenia and dry mouth were reported by more than 10% of the patients but only three discontinued treatment due to AEs [33]. A recent double-blind, multicentre study including 134 chronic daily headache patients who were randomised either to TZN or placebo found the following results after one month of utilisation of TZN: mean reduction in the total headache days of 30% *vs.* 22% for the placebo group; mean reduction of 55% in the number of days with severe pain *vs.* 21%; and mean reduction in the headache index of 54% *vs.* 19%. The mean dosage used was 18 mg/day (range 2–24, SD 6.4, median 20) divided equally over three dose intervals/day. AEs were also reported by >10% of the patients and presented as somnolence (47%), dizziness (24%), dry mouth (23%) and asthenia (19%). Dropouts due to AEs did not differ significantly between TZN and placebo [34].

Nefazodone

Nefazodone hydrochloride is a phenylpiperazine antidepressant with a distinct and atypical mechanism of action. It is a potent, selective 5-HT_2 antagonist that moderately blocks serotonin and noradrenaline/norepinephrine reuptake, with minimal affinity for cholinergic, histaminic or alpha-adrenergic receptors. Nefazodone has been shown to be an effective antidepressant with similar efficacy to other antidepressants. The potency and specificity of its 5-HT_2 antagonism suggests that nefazodone might be particularly effective in the prophylactic treatment of CDH [18].

A recent open-label study involving 52 patients with CM treated with nefazodone (median dose 300 mg/day) for 12 weeks revealed significant improvement for all headache diary measures [18]. During the last month of treatment, 71% of the patients completing the study showed at least a 50% reduction in headache index compared to baseline, and 59% had at least a 75% improvement. Significant improvements were also seen in pain disability index, quality of life and depression. Common mild to moderate AEs reported by 10% or more of the patients included fatigue, nausea, dry mouth, dizziness, sleep disturbance, blurred vision, irritability/nervousness and sedation. These results provide preliminary support for the efficacy of nefazodone in the prophylaxis of CDH, which might be followed by randomised, double-blind controlled studies. It is important to note that it is metabolised by CYP450 3A4 and patients on it cannot be given eletriptan.

Lisinopril

Lisinopril (LSN) is an angiotensin-converting enzyme (ACE) inhibitor frequently used to treat hypertension and heart failure. It is structurally related to enalapril and does not have an indication for the prevention of migraine, although it possesses various pharmacological effects that may be relevant in the pathophysiology of migraine. It blocks the conversion of angiotensin I to angiotensin II, it also alters sympathetic function, inhibits free radical activity and blocks degradation of bradykinin, encephalin and substance P [35]. LSN has a clear potential to migraine prophylaxis because migraineurs present more commonly the ACE DD gene, which codes for a higher ACE activity [19]. LSN was studied in a double-blind, placebo-controlled, crossover trial for the preventive treatment of migraine in 60 patients. The dose used was 20 mg/day divided over two doses and among the 47 patients who completed the study, the decrease of the endpoints hours with headache, days with headache, days with migraine, index of headache severity and doses of symptomatic medications used was moderate (approximately 20%) but significantly different from placebo. The main side effects are cough, hypotension and fatigue. The oral doses of LSN for use in hypertension range from 5 to 40 mg daily (in single or divided doses), with 10 mg daily as appropriate for the initiation of therapy.

Candesartan

A recent double-blind, placebo-controlled crossover study performed in a Norwegian neurological outpatient clinic assessed the efficacy of angiotensin II receptor blocker Candesartan (CST) in the prevention of migraine. Sixty patients went through a placebo run-in period of 4 weeks, followed by two 12-week treatment periods separated by 4 weeks of placebo washout. Thirty patients were randomly assigned to receive one 16-mg CST cilexetil tablet daily in the first treatment period followed by 1 placebo tablet daily in the second period. The remaining 30 received placebo followed by CST. After 12 weeks, the mean number of days with headache was 18.5 with placebo *vs*. 13.6 with CST (p=0.001) in the intention-to-treat analysis (n=57). Some secondary endpoints also favoured CST, including hours with headache (139 *vs*. 95; p<0.001), days with migraine (12.6 *vs*. 9.0; p<0.001), hours with migraine (92.2 *vs*. 59.4; p<0.001), headache severity index (293 *vs*. 191; p<0.001), level of disability (20.6 *vs*. 14.1; p<0.001) and days of sick leave (3.9 *vs*. 1.4; p=0.01), although there were no significant differences in health-related quality of life. The number of CST responders (≥50% response compared to placebo) was 18 (31.6%) of 57 for days with headache and 23 (40.4%) of 57 for days with migraine. AEs were mild and infrequent [20].

Carabersat

Carabersat (CBS) is a new anticonvulsant devoid of cardiovascular side effects with minimal CNS adverse actions, which opens the ATP-sensitive K^+ channels [36]. It has a potential action in preventing migraine as it acts through an inhibition of CSD in cats as well as trigeminal nerve-induced vasodilatation. Its good therapeutic index and the markedly reduced neurological impairments could make it a useful agent for migraine prophylaxis pending efficacy parameters of controlled studies that are underway.

Petasites

Petasites (PTS) is an extract from the plant *Petasites hybridus* (butterbur) found throughout Europe and parts of Asia, which has been used for medicinal purposes for centuries. This compound has been marketed in Germany for migraine and seems to act through calcium channel regulation and inhibition of peptide-leukotriene biosynthesis [37]. Two studies have analysed the possible efficacy of PTS in migraine prophylaxis. The first was a randomised, double-blind, placebo-controlled trial with 50 mg twice daily, which significantly reduced the number of migraine attacks and migraine days per month [38]. Recently another study conducted by Lipton et al. [39] enrolled 245 patients in a 5-month study who received either 50 mg, 75 mg or placebo twice daily. The 4-month mean attack count was reduced by 48% in patients who received 75 mg twice daily while those receiving 50 mg twice daily presented with a 34% reduction and those who have taken placebo 26% (p<0.01). The potential side effects of liver damage and carcinogenesis in animals are thought to be related to the pyrrolizidine alkaloids of butterbur, which were removed in the commercially available presentations. Therefore, the tolerability was excellent although it is contraindicated during pregnancy and lactation [39].

Coenzyme Q10

There has been a recent interest in the role that mitochondria may play in migraine pathogenesis. Clues from magnetic resonance spectroscopy (MRS) [40] studies and DNA analysis [41] suggest that migraine, at least in a subset of individuals, may be the result of mitochondrial impairment. Coenzyme Q10 is a naturally occurring substance and essential element of the mitochondrial electron transport chain [42]. A recent study by Rozen et al. [42] assessed the efficacy of coenzyme Q10 as a preventive treatment for migraine headaches. Thirty-two patients with migraine were treated with coenzyme Q10 at a dose of 150 mg/day. Thirty-one of 32 patients completed the study; 61.3% of patients had a greater than 50% reduction in number of days with migraine headache. The average number of days with migraine during the baseline period was 7.34 and this decreased to 2.95 after 3 months of therapy, which was a statistically significant response (p<0.0001). Mean reduction in migraine frequency after 1 month of treatment was 13.1% and this increased to 55.3% by the end of 3 months. Mean migraine attack frequency was 4.85 during the baseline period and this decreased to 2.81 attacks by the end of the study period, which was a statistically significant response (p<0.001). There were no side effects noted with coenzyme Q10. A recent blinded study showed that 300 mg of coenzyme Q10 was statistically better than placebo in prevention of migraine.

New treatment options

Advances in our understanding of the receptors expressed on trigeminal afferents and the neuropeptides most important in initiating and maintaining the pain of migraine, has led to the development of highly selective receptor targets whose modulation would inhibit the release of these neuropeptides. In this way, the transmission of nociception along peripheral

and central trigeminal pathways would be interrupted and pain would be ameliorated or terminated without the need for or the inherent risks associated with drugs that cause vasoconstriction. Below we briefly review some of these options.

Adenosine has an established antinociceptive effect in humans. Recent findings suggest that the analgesic effect of adenosine may be mediated by the adenosine A1 receptor [43]. The relevance of these findings for human migraine is based on the recent observations that A_1 receptor protein is localised in human trigeminal ganglia and two selective A_1 receptor agonists, GR79236 and GR190178, have been shown to inhibit the peripheral release of CGRP in the cranial circulation as well as at the central trigeminal synapse, thereby preventing activation of central trigeminal neurons [44].

A novel neurotransmitter receptor referred to as opioid receptor-like-1 receptor (ORL1) has been identified. The heptadecapeptide nociceptin/orphanin FQ (N/OFQ – nociceptin) has been identified as the endogenous ligand for the ORL-1 (NOP_1) receptor. However, it does not bind to opioidergic μ-, δ- or κ-receptors [33], nor are the effects of nociceptin antagonised by naloxone [45]. Nociceptin seems to be involved in several biological systems and may play a role in central nociceptive processing [45].

Vanilloid type 1 receptors (VR1) are activated by capsaicin, located on small- and medium-sized neurons that are either unmyelinated C-fibres or thinly myelinated Aδ-fibres, and are present on neurons in the human trigeminal ganglia. VR1 receptor activation may lead to CGRP-induced vasodilation at the trigeminovascular junction, and therefore, the VR1 receptor is potentially a feasible target for the development of anti-migraine compounds [45].

LY293558 is an AMPA/KA receptor antagonist and has been tested for the treatment of migraine and pain. In a multicentre randomised, single-attack study patients received LY293558 1.2 mg/kg iv (n=13), 6 mg subcutaneous sumatriptan (n=15) or placebo (n=16). Of 45 patients who were enrolled in the study, 44 completed it. Two-hour headache response rates were 69% for LY293558 (p=0.017 *vs*. placebo), 86% for sumatriptan 6 mg sc and 25% for placebo [46]. Similar compounds could be developed as preventive agents in migraine therapy.

CGRP is one of several neuropeptides found within the sensory terminals of the trigeminal nerve. Recent data suggests that antagonising the effect of CGRP may provide acute relief of migraine headache [47]. Preventive drugs might be developed on the same principle.

Conclusions

The development of new agents for the prevention of migraine has lagged behind the advances in acute therapy that occurred with the introduction of the triptans. However, new and emerging options, some of them studied in extensive well controlled clinical trials, give hope for the development of future preventive agents. We are clearly in better shape with regard to migraine prevention in comparison to a few years ago. It can be expected that modern neuroscience will provide more efficacious tolerable and safe preventive medications for patients with migraine.

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Menstrual migraine: clinical considerations in light of revised diagnostic criteria

Abstract Menstrual migraine is not formally recognised by the International Headache Society Diagnostic Classification, but "candidate criteria" for its diagnosis have been published. Attacks of migraine occurring in a consistent relationship with menstruation can be classified as "pure" menstrual migraine if they occur at no other time of the month, and as "menstrually related" if other attacks occur throughout the month. It remains controversial whether such attacks are longer, more severe or more difficult to treat than other attacks, but this form of migraine does lend itself to pre-emptive treatment because its timing and trigger can be anticipated. This paper reviews evidence for specific acute and pre-emptive treatment strategies, including the use of hormonal supplementation, scheduled triptans and nonsteroidal anti-inflammatory drugs.

Key words Migraine · Menstruation · Prophylaxis

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Introduction

Menstrual migraine is not recognised as a separate entity in the most widely used diagnostic classification system for headache. Instead, the 2004 revised version of the International Classification of Headache Disorders (ICHD-II) includes "candidate" criteria in the appendix for two entities: menstrual related migraine (formerly called menstrual-associated migraine) and pure menstrual migraine (formerly called true menstrual migraine) [1] (Table 1). These require that to be considered due to menstruation, an attack must occur during an interval from two days before to three days after the onset of menstrual flow (with ovulation as day 0, this would be days –2 to +3). The ICHD further specifies that such attacks must occur in 2 out of 3 cycles.

Entities defined in the appendix of the ICHD are those that are considered to have insufficient validation for inclusion in the formal classification system, and the candidate criteria are suggested as a framework on which research to confirm or refute the disorder can be based. Using definitions similar but not identical to those contained in ICHD II, Edelson in 1985 reported that approximately 60% of women with migraine noted that headaches were more likely to occur in association with the menstrual period, although only 14% had headaches in association with menstruation and at no other time of the month. Slightly over 40% of women with migraine noted no correlation between their headaches and menstrual periods [2]. The validity of patient self-report of a migraine diagnosis, particularly one that requires attacks to occur within a 5-day monthly window, is in question, and thus these data may overestimate the true prevalence of menstrually related and pure menstrual migraine. For this reason, ICHD-II authors commented that "documented prospectively recorded evidence, kept for a minimum of three cycles, is necessary to confirm the diagnosis as many

Table 1 Provisional ICHD-II criteria for menstrual and nonmenstrual migraine [1]

A1.1.1 Pure menstrual migraine without aura

Diagnostic criteria

A. Attacks, in a menstruating woman, fulfilling criteria for 1.1 *Migraine without aura*

B. Attacks occur exclusively on day 1±2 (*ie*, days –2 to +3) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle

A1.1.2 Menstrually related migraine without aura

Diagnostic criteria

A. Attacks, in a menstruating woman, fulfilling criteria for 1.1 *Migraine without aura*

B. Attacks occur on day 1±2 (*ie*, days –2 to +3) of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle

A1.1.3 Nonmenstrual migraine without aura

Diagnostic criteria

A. Attacks, in a menstruating woman, fulfilling criteria for 1.1 *Migraine without aura*

B. Attacks have no menstrual relationship

women over-report an association between attacks and menstruation" [1].

Many important but underappreciated difficulties arise in trying to determine the prevalence and impact of menstrually caused migraine attacks. To begin with, some attacks that occur in the specified menstrual time window are due to chance, and are only temporally, but not causally, related to menstruation. Then, too, most triggers of migraine are not so powerful that they cause a headache to happen in each instance [3]. There is no reason to suppose that hormonal triggers are different. This variability makes study of triggers in general quite difficult, and this is especially true in the case of menstrual-associated migraine attacks. There is also no agreement on the time period over which a trigger can exert its influence, and this problem is compounded by the fact that the menstrual flow, on which determination of the label "menstrual migraine" depends, is in fact only an imperfect reflection of the underlying oestrogen decreases that are presumably triggering the attack in the first place [4]. Confusion about the nature of the trigger is also apparent if one reads the ICHD-II classification closely. The authors make the somewhat confusing suggestion that if menstrual migraine is felt to be due to "exogenous" oestrogen withdrawal (presumably oral contraceptives), both menstrual migraine and oestrogen-withdrawal headache should be recorded [1]. The menstrual window of –2 to +3 days recommended by ICHD-II has the merit of precision, but is quite arbitrary. Finally, we lack biomarkers that might be useful in more precisely defining the relationship between hormonal fluctuations and headache. Oestrogen levels, for example, are difficult to measure, and in any case it is probably not the absolute level of oestrogen that is important but rather both the rate and magnitude of any decline, and further, even the level and duration of high oestrogen levels preceding that decline [5].

Current treatment of menstrual migraine

Acute therapy of menstrual migraine is similar to that of nonmenstrual migraine, with the exception that nonsteroidal anti-inflammatory drugs (NSAIDs) are perhaps more likely to be used, in recognition of the role of prostaglandins in other menstrual-related symptoms. Ergot derivatives and triptans as well as nonspecific medications such as butalbital compounds and opioids are also employed.

In contrast to acute therapy, which begins after headache onset, preventive therapy is used to prevent attacks, shorten attacks, or increase the effectiveness of acute therapy. Short or long-term prophylactic therapy with NSAIDs, ergot derivatives, specific serotonin reuptake inhibitors (SSRIs), calcium channel blockers and magnesium supplements have all been advocated [6]. Naproxen sodium in a dose of 550 mg bid has been best studied [7, 8]. Some authorities advocate perimenstrual increases in the dose of preventive agents being used throughout the month, while others advocate the use of short-term perimenstrual prophylaxis only around the menstrual period. The latter is often recommended for women whose menstrual-related headaches alone are resistant to therapy [6].

Because oestrogen withdrawal is widely viewed as the cause of menstrual-associated migraine, oestrogen supplementation to prevent or blunt the premenstrual fall in oestrogen levels has gained in popularity. Somerville [9] was not successful in using oestradiol implants, although Magos et al. [10] obtained different results and also showed efficacy of a cutaneously applied oestrogen gel. There may be a critical level of oestrogen necessary for efficacy. That this is the case is suggested by a study done by Pradalier et al [11], in which 25-μg patches were not

effective in preventing menstrual migraine, while 100-µg patches were. Still other studies found that the 50-µg patch was not effective [12].

Other recommended prophylactic hormonal treatments for refractory menstrual migraine are based largely on the results of expert experience or small, open-label trials. Among those sometimes advocated are the use of bromocriptine [13], tamoxifen [14, 15], danazol [16] and gonadotropin-releasing hormone analogues with add-back oestrogen therapy. The risk to benefit ratio of oestrogen supplementation has not been fully demonstrated.

Migraine occurring in association with menstruation is perceived by many patients and physicians as being longer, more severe and more resistant to treatment. Often one hears it said that there are patients whose nonmenstrual headaches respond well to traditional prophylactic therapy for migraine but whose menstrual attacks continue. In fact, this widely held view is hard to substantiate. Stewart et al. reported results of a population-based study in which 81 women recorded 7219 diary days over 3 menstrual periods. This study did show a significantly elevated risk of migraine on days 0 and 1, for migraine without aura, and although headache intensity was slightly higher, the duration, disability score and symptom score for menstrual-associated headaches was no different from nonmenstrual headaches [17]. One explanation for this striking discrepancy between expert opinion and population studies may be that specialists regularly come in contact with a small, vocal group of patients whose headaches, menstrual or otherwise, are refractory to traditionally employed therapies. This patient population is not representative of the larger group of women in the population with migraine, however.

One benefit of many of the large-scale triptan trials has been the ability to perform *post hoc* analyses of the large databases generated. Because patients in most trials recorded information about menstrual periods, the efficacy of triptans in the treatment of menstrual attacks could be compared with their efficacy in treating nonmenstrual attacks. Despite patient and physician perception that menstrual migraine is more resistant to treatment than other migraine attacks, analyses of these large databases for many different medications uniformly show no difference in efficacy for menstrual or nonmenstrual attacks.

For example, rizatriptan [18], zolmitriptan [19], sumatriptan [20] and eletriptan [21] have all been shown to be equally effective in menstrual and nonmenstrual migraine when the endpoint is headache relief. Similar information exists for the nonspecific combination analgesic Excedrin (aspirin-caffeine-acetaminophen) [22]. The weight of the evidence thus stands in complete contradiction to the oft-repeated clinical impression that acute migraine treatment is less effective for menstrual than for nonmenstrual headaches.

Increasing familiarity and comfort with the triptans for the abortive treatment of migraine has led to interest in their use for prophylactic, or preventive, treatment of migraine. Much of this interest has centred on their use for short periods of time on a regular basis to prevent migraine predictably associated with the menstrual period, so-called "menstrual migraine". It has long been recognised that in a subset of women with migraine, menstruation appears to be a powerful trigger for attacks. In part, interest in using the triptans prophylactically for menstrual migraine stems from the perception (shown in the previous section of this paper to be counter to the weight of evidence) that menstrual migraine is somehow more severe than other forms of migraine and responds less well to acute treatment, even with triptans.

Until the advent of the triptans, attempts at perimenstrual migraine prophylaxis primarily involved scheduled use of NSAID medications. These are relatively inexpensive medications that have efficacy in other symptoms frequently associated with menstruation, such as dysmenorrhoea. Level B evidence (one randomised, controlled trial supporting efficacy) supports the use of naproxen sodium 550 mg po bid from days –7 to +6. In 1998, Newman published the results of an open-label study using sumatriptan 25 mg tid on a scheduled basis in women with menstrual migraine [23]. This study is in large part responsible for an increase in enthusiasm for the use of triptans in the treatment of menstrual migraine.

Established prophylactic medications for migraine (such as beta blockers, tricyclic antidepressants, sodium valproate, methysergide) are generally reserved for patients who have either very frequent attacks or whose attacks do not respond well to acute treatment [24]. In similar fashion, the use of triptans for menstrual migraine prophylaxis, if demonstrated to be effective, would likely be reserved for patients whose headaches did not respond to traditional treatment.

Newman and others reported the results of trials of naratriptan 1 mg po bid compared with 2.5 mg po bid and placebo administered perimenstrually from days –2 or 3 to +3. While the 1 mg dose showed statistical superiority to placebo, the results were modest, and the 2.5 mg dose showed no difference from placebo with respect to headache severity, productivity or migraine-related quality of life [25, 26]. A recent review of the evidence supporting the use of short-term preventive strategies for menstrual migraine found multiple randomised, controlled trials supporting efficacy for oestradiol gel 1.5 mg applied from days –2 to +5 and for the naratriptan regimen mentioned above [27]. A regimen using a double loading dose followed by 2.5 mg frovatriptan bid for 6 days perimenstrually recently showed a 23% therapeutic gain compared with placebo on the measure of headache prevention [28]. Targeted perimenstrual prophylaxis of menstrually triggered migraine attacks thus holds promise, but the number of women who would benefit from this treatment remains unclear, as do harm to benefit evaluations and information about the long-term safety of such regimens [29].

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Advanced strategies of short-term prophylaxis in menstrual migraine: state of the art and prospects

Abstract Patients suffering from menstrual migraine (MM) may be ideal candidates for an intermittent prophylaxis, usually termed short-term or mini-prophylaxis. It covers the whole period of vulnerability, e.g., the perimenstrual period, starting some days before the expected onset of MM attack. Theoretically MM attacks are an optimal target for drugs specifically developed for acute head pain. Unfortunately, due to their particular tendency to be longer, more intense and less responsive to analgesics, symptomatic approaches alone are not often able to completely control pain and its correlates. Many drugs have been proposed for short-term prophylaxis of MM. In this paper we analyse only non-steroidal anti-inflammatory drugs, coxibs and triptans (especially those with longer half-life, naratriptan and frovatriptan). Moreover, MM can be prevented by a variety of hormonal manipulations, including oral contraceptives, which may be administered with an extended-dosing strategy; oestrogen replacement therapy; antioestrogen agents (danazol, tamoxifen); gonadotropin-releasing hormone agonists followed by oestrogen add-back therapy. Finally, the use of some products, such as magnesium and phytoestrogens, that probably meet the requirements of those patients that appreciate a more "natural" approach, is discussed.

Key words Coxibs • Short-term prophylaxis • Hormones • Menstrual migraine • NSAIDs • Triptans

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Introduction

Menstrual migraine (MM) often represents a challenge for the headache specialist [1]. Theoretically MM attacks are an optimal target for drugs specifically developed for acute head pain [2]. Unfortunately, due to the particular tendency of the attacks appearing in the perimenstrual period (PMP) to be longer, of higher intensity and less responsive to analgesics [3], often symptomatic approaches alone are not able to totally control pain and its correlates (e.g., accompanying symptomatology and disability). In these cases, MM patients may be ideal candidates for an intermittent prophylaxis, usually termed short-term or mini-prophylaxis, that covers the whole period of vulnerability, e.g., the PMP, starting some days before the expected onset of MM attack days before. In order to start a cyclic prophylaxis, the predictability of the attacks is mandatory; that is, MM patients need to have regular menstrual cycles and a good diary card (at least three consecutive menstrual cycles should be monitored) of their headaches, particularly of those in relation to the PMP.

MM probably has a pathophysiological background different from that of other types of migraines, the neuroendocrine changes associated with the menstrual cycle being the key factor that predisposes to the attacks. The decrease in oestrogen levels during the late luteal phase of the cycle is the main predisposing factor, as suggested by Somerville [4]. In support of this theory, other hormonal events that result in falling oestrogen after sustained high levels can cause migraine attacks. A high percentage of migrainous

women experience pain relief during the course of pregnancy, when oestrogen levels gradually rise, but migraine can recur immediately postpartum, when oestrogen levels rapidly decrease. Women taking combined oral contraceptives (COCs) experience migraine during the pill-free week, when oestrogen falls after three weeks of high levels [5]. Declining oestrogen levels have been hypothesised to affect pain receptors and blood vessels in the brain, sensitising them to other biochemical factors involved in producing headache [6, 7]. Close interrelationships exist between oestrogens and neurotransmitters, especially the catecholamines, noradrenaline, serotonin and dopamine. Decreases in endorphins may also occur with reduced levels of oestrogen; furthermore, an increased production of prostaglandins (PGs), particularly of the oestrogen type, associated with an imbalanced ratio between prostacyclin and thromboxane A_2, may be directly involved in the development of MM [8].

The pathophysiological concepts briefly mentioned above directly suggest the use of several drugs in the cyclic prophylaxis of MM.

Short-term prophylaxes of MM

The following methods can be tried, if a specific prophylaxis is indicated. This applies for the prevention of all types of MM, both in the case of pure MM and of menstrually related migraine, when this last does not respond to usual prophylactic treatments of migraine.

Each regimen should be used for at least 3 cycles before being deemed ineffective. It is noteworthy that none of the drugs and hormones recommended are licensed for cyclic MM management [5]. Moreover, a cyclic prophylaxis has two major disadvantages: (1) if the patient become pregnant, teratogenic effects of the drugs cannot be excluded; (2) the method can be applied properly only in the presence of quite regular menstrual cycles. This last limitation could however be overcome by teaching women under cyclic prophylaxis to take their basal temperature daily (or to use a urine-based ovulation prediction tests) in order to recognise ovulation and subsequently establish when the drug intake should begin.

NSAIDs and coxibs

Non-steroidal anti-inflammatory drugs (NSAIDs) are potent PGs inhibitors; they are usually recommended first because they are effective, generally well tolerated and reasonably priced. Moreover, they present the advantage of preventing also other forms of perimenstrual pain, such as dysmenorrhoea.

Some studies suggested naproxen sodium 550 mg once (or twice) daily, starting from 7 days before the expected onset of menstruation for a total of 13–14 days, could be effective both in the treatment of pure MM [9] and menstrually related [10] migraine. Mefenamic acid (500 mg bid) or fenoprofen (600 mg bid) started either 2–3 days before the expected onset of menstruation or on the first day of bleeding have been suggested for reducing migraine and associated dysmenorrhoea [1, 5]. NSAIDs, however, may not be well tolerated and can produce gastrointestinal irritation. Coxibs, a class of selective cyclooxygenase-2 inhibitors, show anti-inflammatory and analgesic properties, and a significantly improved gastrointestinal tolerability profile. Rofecoxib at a perimenstrual daily dose of 25 or 50 mg caused a significant reduction of MM frequency in a small open-label trial [11]. Also celecoxib (200 mg/day for 7–10 days starting 2 days before the expected onset of menses) significantly reduced the number of days with MM and the need for analgesics [12].

Triptans

Since 1998, when Newman et al. [13] proposed oral sumatriptan (25 mg tid, given for a total of 5 days in the PMP) as mini-prophylaxis therapy for the menstrual attack, the attention of some researchers has been focused on the use of triptans for this specific aim. In the first open pilot study, in 126 sumatriptan-treated cycles, migraine was absent in 52.4% and significantly reduced in severity in 42%. Breakthrough headaches were rare and significantly reduced in severity compared with baseline headaches.

Recently new triptans, like naratriptan and frovatriptan, with longer half-life and a low risk of recurrence, have been thoroughly evaluated for MM prophylaxis.

A randomised, double-blind, three-arm, parallel-group, placebo-controlled study [14] tested the efficacy of naratriptan as mini-prophylaxis of MM in women suffering from menstrually related migraine. Two dosages (2.5 or 5 mg) or placebo were administered twice daily for 5 days starting 2 days before the expected onset of MM for 4 PMPs.

Compared with placebo, naratriptan 1 mg reduced the number of MMs and MM days.

Across all treated PMPs, more patients were headache-free with 1 mg naratriptan compared with those in the placebo group. The 2.5 mg dose of naratriptan was not statistically superior to placebo for any measure.

Moschiano et al. [15] recently conducted the first trial on the use of naratriptan in short-term prophylaxis of pure MM. This was an open-label pilot study, administering 1 mg naratriptan twice daily for 6 days, starting 2 days before the expected onset of menses. Patients, after an observation period of 3 months free from prophylactic

treatment, underwent naratriptan mini-prophylaxis for three consecutive menstrual cycles. The mean number of pure MM attacks decreased from 3.5±1.4 in the 3-month observation period to 1.6±1.3 in the 3-month treatment with naratriptan. The percentage of responders (subjects who recorded a decrease – equal or more than 50% – in the mean number of attacks) was 61.4%.

Silberstein et al. [16] conducted in a group of patients suffering from menstrually related migraine a randomised, double-blind, placebo-controlled, three-way crossover design study, treating each of three PMPs with placebo, frovatriptan 2.5 mg qd and fovratriptan 2.5 mg bid. Frovatriptan was taken for 6 days beginning 2 days before the expected onset of MM. The incidence of MM during the 6-day PMP was 67% for placebo, 52% for frovatriptan 2.5 mg qd and 41% 2.5 mg bid. The bid regimen was superior to the qd regimen. Both frovatriptan regimens were superior to placebo, and reduced also MM severity, duration and the use of rescue medication.

The mechanisms through which the triptans exert their positive prophylactic action on MM remain unclear: they may act peripherally to prevent the neurogenic inflammation that occurs during the PMP, with declining oestradiol levels [4] and rising PG levels [8].

Even if issues such as potential for rebound migraine, unresolved cost and safety concerns dictate that cyclic prophylactic therapy has to be reserved exclusively for really unresponsive MM cases [17], the mini-prophylaxes will probably represent an important field of clinical application in the future, particular for long half-life triptans. In any case, triptans would have to show compelling advantages over other therapies to be a plausible prophylactic treatment for MM.

Hormonal manipulations

If oestrogen withdrawal is a suspected causative mechanism, attacks can be prevented by stabilising oestrogen levels during the late luteal phase of the cycle [5].

Oestrogen replacement in the PMP has been tried with oral tablets, subcutaneous implants, percutaneous gel or transdermal patches [18]. At present, the application of oestradiol percutaneous gel seems to be the best treatment, providing the most stable blood steroid levels. In fact, adopting an individual posology, this route of administration allows the maintenance of constant and effective oestradiol levels, without provoking either an initial supraphysiological increase, like the injectable formulation does, or short daily oscillations, as occurs with the oral route. The effectiveness of the oestradiol cutaneous patch, even if it provides stable plasma oestrogen levels and has anecdotally been reported to be effective, is controversial [19].

In most cases, the use of COCs in migrainous women concentrates migraine attacks in the withdrawal week, allowing the prescription of a short-term prophylaxis. In selected cases of intractable MM appearing in the pill-free week, the continuous intake of COCs for 42 or 63 days can reduce the number of menstrual attacks. Furthermore, an upcoming contraceptive formulation on the market allows having only 4 periods each year, instead of the traditional 13. It contains the same hormones as traditional oral contraceptive pills, with a combination of ethinyl oestradiol and levonorgestrel; women take the active pills for 84 consecutive days, followed by 7 consecutive placebo days. This dosing schedule should theoretically reduce MM to 4 episodes per year, but this statement needs to be supported by objective studies.

In order to prevent MM, oestrogen levels can be stabilised also using treatments that suppress the cycle by reducing oestrogen levels [18]. Danazol, which inhibits ovarian stetroidogenesis, suppressing the pituitary-ovarian axis, produced benefit in 63% of 131 women with MM when administered in doses of 200 mg twice a day from the 3rd to the 28th day of the cycle [20]. Sixteen percent of the patients withdrew because of side effects. In a small open study on 8 cases of severe MM [21], tamoxifen, another antioestrogen agent, proved markedly effective in 5 patients and achieved mild to moderate results in 2 cases, while 1 patient did not respond at all. Controlled studies on tamoxifen and other oestrogen receptor selective modulators (e.g., raloxifen) are warranted.

Two case series and one case report evaluated the role of gonadotropin-releasing hormone (GnRH) agonists with and without oestrogen add-back therapy in the prevention of MM [22]. All three studies suggested that both the GnRH agonist+oestrogen and GnRH agonist+placebo treatments prevented pure MM or menstrually related migraine.

In one recent study [23] on migrainous women (not only those suffering from MM), medical oophorectomy, obtained with a subcutaneous goserelin implant, followed by the addition of transdermal oestradiol, provided a modest preventive benefit (33.7% reduction of Headache Index) in comparison to the run-in period, while the use of goserelin alone was inadequate to prevent headache. Moreover, the decrease in Headache Index in the goserelin+oestradiol group was secondary to an improvement in headaches throughout the menstrual cycle and not just secondary to an effect on perimenstrual headaches. These data suggest that the minimisation of hormonal fluctuations could interfere only in headaches related to the menstrual cycle, while headaches outside the PMP need also a high stable level of oestradiol to be prevented. In any case, medical oophorectomy is not a benign therapy, as it provokes a functional menopause, with typical side effects. Many of these side effects could be prevented by oestrogen add-back therapy, but a long-term therapy would

require the addition of a progestin, to prevent endometrial hyperplasia or cancer or both. In conclusion, until further large-scale studies with a combination of GnRH antagonist+oestrogen+progestin have been conducted, documenting the long-term safety and the real benefit on headache, this type of therapy is not recommendable, even in the case of intractable MM.

Other treatments

Many other pharmacological approaches have been attempted to prevent MM: they are described in more complete reviews on the matter [5, 18, 24].

We would like to mention only two other possible therapeutic options, magnesium and phytoestrogens, that probably meet the requirements of those patients that appreciate a more "natural" approach.

Magnesium (Mg) pirrolydone carboxylic acid (360 mg/day by oral route) was evaluated in a double-blind, placebo-controlled study in 20 patients suffering from MM [25]. The treatment started on the 15th day of the cycle and continued till the next menses. Pain Total Index was decreased by both placebo and Mg, with patients receiving active drug showing significantly lower values. The number of days with headache was reduced only in the active drug group. Mg also improved premenstrual complaints.

Two studies tried the use of phytoestrogens in the prevention of MM. Forty-nine patients were randomised by Burke et al. [26] to receive in a continuous manner either placebo or a daily combination of 60 mg soy isoflavones, 100 mg dong quai and 50 mg black cohosh. Average frequency of MMs was significantly reduced in patients treated with the phytoestrogen preparation in comparison with placebo-treated group. In a small group (n=11) of pure MM sufferers, Ferrante et al. [27] administered a perimenstrual cyclic prophylaxis with 56 mg genisteine and 20 mg diadzeine per day. The average number of days with migraine decreased significantly after 3 months of therapy.

Preventive natural strategies of MM probably deserve greater attention; objective studies on wider populations are urgently needed.

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Topiramate in migraine prophylaxis

Abstract This paper reviews results of placebo-controlled trials on topiramate (TPM) prophylaxis in migraine patients, and discusses issues regarding the use of this medication in clinical practice. Data from well conducted double-blind controlled trials and from a comparative trial show that TPM is effective against migraine, confirming the experience of physicians in various countries. Lack of major contraindications, high responder rate, good tolerability at the target dose (100 mg/day) following slow titration, and lack of weight gain make TPM one of the most effective and well accepted drugs for migraine prophylaxis.

Key words Migraine • Topiramate • Prophylaxis • Clinical trial • Clinical practice

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Introduction

Migraine is a heterogeneous condition producing a range of impacts of variable severity on personal and social functioning [1, 2]. Migraine patients with high attack frequency, severe and disabling pain, poor response to acute treatment, or who overuse acute medications, are candidates for prophylactic treatment [3, 4].

While acute treatments should be taken only during attacks to reduce the severity and duration of the crises, prophylactic treatments should be taken every day, their aim being to reduce the frequency as well as the duration and severity of attacks, and ultimately to improve quality of life and ability to function in daily activities [3, 5].

Health-related quality of life during headache-free periods is poor in migraineurs compared to people without migraine, and also seems to be worse than experienced by people with other chronic disorders (myocardial infarction, diabetes and hypertension) [6–8]. In an Italian study on 264 consecutive patients with migraine without aura attending a headache centre [9], disability was found to affect all daily activities in the three months prior to examination: productivity at work was reduced by 50% or more on 6.6 days, and 2.2 work days were missed. Total or partial disability also affected non-work activities, with household work missed on 4.9 days, productivity in performing household work reduced by 50% or more on 4.6 days, and family/social/leisure activities missed on 5 days. In the second American Migraine Study [10], 53% of the migraineurs surveyed reported that their severe headaches led to substantial impairment of daily activities and bed rest in many cases.

Many treatments are currently used for migraine prophylaxis, including β-blockers, calcium channel antagonists, serotonin antagonists, antidepressants and antiepileptics [11, 12]. However, many of the studies conducted with these drugs did not adhere to the criteria proposed by the International Headache Society [5] or the US Headache Consortium guidelines [3] for conducting

headache trials. These criteria stress that preventive treatments should be validated using evidence-based standards, and in particular efficacy should be supported by data from large, well designed, placebo-controlled trials; data should support a sustained prophylactic efficacy; safety and tolerability should be assessed; side effects should not impede compliance; treatment should either improve or not worsen comorbid conditions.

Topiramate (TPM) has emerged relatively recently as a treatment for migraine prophylaxis. The exact mechanisms by which TPM is effective in migraine have not been established, however multiple effects of the drug have been documented, several of which may contribute to effective migraine prophylaxis. In particular the drug enhances the inhibitory effects of GABA, blocks the excitatory effect of glutamate, blocks Na^+ channels limiting repetitive firing, reduces Ca^{2+} channel activity and inhibits carbonic anhydrase [13, 14]. TPM bioavailability is >80%. Maximum plasma levels (C_{max}) are reached 1.3–1.7 h after oral administration, and half-life is 19–23 h. Protein binding is around 15%; 50%–80% of the drug is excreted unchanged in the urine.

This paper briefly reviews the results of large, well conducted placebo-controlled trials of TPM in migraine patients, and discusses issues arising from the use of this medication in clinical practice.

Topiramate in migraine trials

Clinical data supporting the efficacy of TPM in migraine prophylaxis are more robust than for many of the drugs currently used to prevent migraine. Following small double-blind studies, three randomised, double-blind, placebo-controlled trials were conducted to determine the efficacy of TPM in migraine prevention.

The two pivotal studies were MIGR-001, conducted at 49 sites in the USA on 469 patients, and MIGR-002, conducted at 52 US and Canadian centres on 468 patients [14, 15]. In both these studies patients were randomised to placebo or to TPM at various daily doses (50, 100 or 200 mg) for 26 weeks. In all cases, TPM was started at 25 mg/day and titrated to target dose or maximum tolerated dose at the rate of 25 mg/week. Efficacy was assessed throughout the double-blind period, including the titration period. The primary efficacy measure was change in mean monthly migraine frequency compared to baseline. Intent to treat analyses showed that TPM (100 mg/day and 200 mg/day) was associated with significant reductions in monthly migraine frequency compared with placebo, while in the 50 mg/day arm the reduction in migraine frequency was not significantly different from that of the placebo arm. About half the responders in the 100 and 200 mg/day arms had a 50% reduction in migraine frequency, while in the other half the reduction was ≥75%. The effect became evident during the first month of treatment. TPM use was also associated with significant reductions in acute medication usage.

The MIGR-003A trail was a randomised, double-blind, multicentre comparative trial (61 sites in 13 countries) on 575 migraine patients. It was designed to assess the efficacy and safety of TPM *vs*. placebo in migraine prophylaxis, and used propranolol as the active control [16]. Patients were randomised to TPM (100 or 200 mg/day), propranolol (160 mg/day) or placebo. TPM was found superior to placebo in reducing monthly migraine frequency (overall 50% responder rate, with reduced rescue medication use). The 100 mg/day TPM and propranolol groups were characterised by similar reductions in migraine frequency, responder rate and daily rescue medication usage. TPM 100 mg/day was better tolerated than TPM 200 mg/day. No unusual or unexpected safety risks emerged.

Based on these results it was concluded that 100 mg/day of TPM is effective in reducing migraine frequency and that 200 mg/day does not provide additional benefits. The target dose of TPM in migraine prophylaxis was therefore recommended as 100 mg/day. This dose level was also associated with good tolerability. The most common adverse event was paraesthesia (in ~50% patients), which was usually mild to moderate, although treatment limiting in 8% of patients; fatigue affected 5% of patients. These studies also revealed a low incidence (6%–7%) of adverse CNS events in migraine patients (somnolence, insomnia, memory difficulties, concentration difficulties, language problems and mood changes). In addition, 60%–70% of patients on TPM lost weight, with no change in body weight occurring in 20%. The mean overall reductions in baseline body weight in each MIGR trial were 3.8, 3.3% and 2.7% respectively.

Topiramate in clinical practice

Based on the findings of the trials discussed above, TPM is considered suitable and effective for the prevention of migraine in clinical practice. It satisfies the currently accepted criteria for preventive treatments [4, 5]. Efficacy onset is generally rapid and the effect is sustained; safety and tolerability are satisfactory; at recommended doses, side effects are acceptable and generally well tolerated. In addition, two particular characteristics (does not worsen comorbid conditions; does not promote weight gain) suggest TPM should be considered as first-line prophylactic treatment for migraine. The available drugs for migraine prevention are characterised by diverse indications, contraindications and side-effect profiles which must be weighed for each individual patient. TPM can be used in

the presence of numerous comorbid conditions which contraindicate the use of other migraine prophylactics: asthma contraindicates β-blockers; excess weight contraindicates amitriptyline and flunarizine; heart block, epilepsy and urinary retention contraindicate amitriptyline; liver disease and bleeding disorders contraindicate valproate; depression contraindicates flunarizine and β-blockers. Weight gain is the most common adverse event associated with other antimigraine therapies, and may be a key factor in patient non-compliance, particularly in women. TPM is the only drug for migraine prophylaxis that is unlikely to cause weight gain and often causes modest weight loss.

In Europe, the prevalence of obesity ranges from 10% to 20%, while marked increases in the prevalence of obesity have been recorded recently and some projections suggest that up to 50% of the European population could be obese within a generation [17, 18]. Various disorders, including several serious conditions, are clearly related to obesity and being overweight (examples include type 2 diabetes, hypertension, coronary heart disease, osteoarthritis, endometrial cancer and gall bladder disease). Being overweight also correlates with hypertension, hypercholesterolemia and high blood triglycerides – themselves independent risk factors for cardiovascular and other conditions. Treatment-induced weight gain is therefore much more than a cosmetic issue.

Another important advantage of TPM is that, up to 200 mg/day, it does not interact with sumatriptan, amitriptyline, propranolol or oral contraceptives.

Experience with TPM in the treatment of epilepsy and migraine has shown that low initial dosing and slow titration increase tolerability. Our clinical experience is that by starting at 25 mg/day and increasing at 25 mg/week, it is possible to reach a maintenance dose of 50 mg bid in most patients; it is also usually possible to increase the daily dose to 150 or 200 mg, if necessary.

Other side effects may occur rarely. Metabolic acidosis is a possibility when predisposing conditions are present. Such conditions include renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet and use of other carbonic anhydrase inhibitors. Hyperthermia may occur, especially in children doing physical exercise, or after exposure to high ambient temperature. Kidney stone formation is a rare adverse event. Attention to adequate hydration in patients treated with TPM is recommended to minimise the risk of these unusual side effects. Acute myopia and secondary angle-closure glaucoma syndrome are other possibilities: they are rare, easily recognisable, and reversible following TPM withdrawal; pre-screening is not recommended.

A questionnaire survey of 30 headache specialists from different countries was recently conducted to determine practice with regard to migraine prophylaxis, and first-, second- and third-line treatment options [19]. TPM was considered by many clinicians as first-line (more than 20%) or second-line treatment (about 15%).

Conclusions

The effectiveness of TPM as a migraine preventive was established through the largest randomised, double-blind, placebo-controlled trial programme carried out so far in the field of migraine. These trials were characterised by enrolment across countries, intention-to-treat analyses and trial duration sufficiently long to adequately assess effect. TPM is the only drug used in migraine prevention which is not likely to cause weight gain; this, together with high responder rate and acceptable adverse event profile, has caused the drug to be well accepted by migraineurs. Furthermore, TPM's efficacy is supported by its already extensive use in clinical practice: many headache specialists prescribe TPM to migraineurs, both in the USA and Europe.

These favourable characteristics raise the possibility that TPM may have the potential of reducing the personal and social burden of migraine. An ongoing multicentre trial (PROMPT) is assessing whether TPM treatment can improve quality of life and ability to function in daily activities in migraineurs, by comparing scores obtained with validated patient-reported instruments (MIDAS, HIT6, SF-12) before and after TPM prophylaxis. PROMPT is also expected to provide information on long-term use of TPM. There are two study phases. During the first 6 months, period patients receive open label TPM, and the optimal individual dose is approached slowly. In the second double-blind phase, patients are randomised either to their optimised TPM dose or to placebo for 6 months.

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T.N. Ward • M. Levin

Headache in giant cell arteritis and other arteritides

Abstract Giant cell arteritis remains the most common systemic vasculitis in patients over the age of 50. Headache is the most common symptom, but is not invariably present. The headache may take almost any form, and may resemble any of the primary headaches, even cluster. Prompt diagnosis is important to prevent the well known serious complications. Accurate diagnosis allows appropriate therapy. Other forms of vasculitis may also cause headaches so correct diagnosis is essential as therapies may differ.

Key words Arteritis • Giant cell • Vasculitis • Horton's disease

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Giant cell arteritis (GCA), also known as cranial arteritis, temporal arteritis and Horton's disease has probably been present for centuries. There is a suggestive description in a lost text by Ali ibn Isâ from the 10th century describing a man with heat/inflammation of the temporalis muscle and loss of sight [1]. Hutchinson [2] in 1890 published a case of a man with painful inflamed temporal arteries, which prevented him from wearing his hat. The disease was finally clearly defined by Horton et al. [3] in 1932.

While this disease is best known for headache, the 1932 report described 2 cases neither of which had headache. The patients had fever, weakness, anorexia, weight loss, anaemia, mild leukocytosis and tender temporal arteries. Symptoms had been present for 4–6 weeks. Temporal artery biopsy revealed chronic periarteritis and arteritis with granulomas in the adventitia, round cells in the media and in the adventitia of the vasa vasorum. Haemorrhage was present in the media and the intima was thickened. The lumen was partially occluded by thrombi. The authors noted that the history, clinical course and pathology were different than periarteritis nodosum and thrombo-angiitis obliterans. They concluded "it is apparently a focal localisation of some unknown systemic disease" [3].

By 1937 headache had been recognised as a prominent symptom, and by 1938 Jennings had emphasised the risk of visual loss [4, 5]. Steroids were not available until 1949, so unfortunately the natural history of the illness was well described [6]. In 1972 Dalessio again noted the difference from periarteritis and lupus, but also noted the pathology was indistinguishable from Takayasu's arteritis [7]. He referred to the work of Dr. Eng Tang at Scripps clinic, suggesting GCA was an immunologic vasculitis.

GCA commonly occurs in patients over the age of 50, with an erythrocyte sedimentation rate (ESR) over 50 mm/h. It is more common in Caucasians, at higher latitudes, in females, and particularly seems to affect Scandinavians and the British [8]. The prevalence in those over 50 years of age is 133/100 000 [9]. It may be under-

diagnosed, having been found in 1.7% of a consecutive autopsy series [9]. It is the most common primary systemic vasculitis in the elderly [10].

Headache in GCA is the initial symptom in 48% of patients, and is eventually found in 90%, making it the most common manifestation [11]. It may be any type of headache, constant or intermittent, and may mimic tension-type headache, migraine or even cluster [4, 12]. It may be of variable location and severity. This is also true for headache due to other arteritides, which makes accurate diagnosis essential. The headache of GCA usually subsides promptly with initiation of steroid therapy. Other symptoms includes tender temporal artery in 69%, jaw claudication in 67%, polymyalgia rheumatica (PMR) in 48%, weight loss in 55%, fever in 21% (and GCA may present as a fever of unknown origin), absent temporal artery pulse in 40%, visual symptoms in 40%, peripheral joint pain in 21%, tongue claudication in 7%, pain on swallowing in 7% and limb claudication in 5% [9, 13]. Jaw and dental symptoms have caused diagnostic confusion [14].

Other physical findings and symptoms in GCA include signs of temporal artery inflammation (erythema, tenderness, nodularity, thickening, diminished pulsation). It has been noted that the headache of GCA often resolves upon temporal artery biopsy [15]. One-third of patients may have arterial bruits and/or diminished peripheral pulses. Involvement of the aorta may lead to aortic aneurysm, dissection, aortic regurgitation and even aortic rupture. A partial Horner's syndrome may be found, as may a tender carotid artery. Rarely there may be tongue or scalp necrosis. Other findings include neuropathy, vertigo, tremor, tinnitus, myopathy, seizures, anosmia, myelopathy, stupor and coma [9, 16].

The best known dreaded complications of GCA include blindness and stroke (more often involving the posterior circulation/vertebral arteries). When there is ocular involvement without any systemic symptoms/signs the presentation is known as occult GCA. The ophthalmologic complications of GCA include amaurosis fugax (14%), visual loss, diplopia, ptosis, formed visual hallucinations, orbital bruits and acute ocular hypotony [17]. Intraocular vessels, as intracranial vessels, are not involved as they lack an internal elastic lamina. In the pre-steroid era, blindness occurred in up to 60% of patients in some series. Involvement of the posterior ciliary arteries is more frequent than the central retinal artery. Sudden blindness as a presenting symptom is rare. Twenty-five per cent of patients manifesting ophthalmoplegia may go on to blindness if untreated. Fixed visual loss does not improve, and blindness may occur despite the initiation of steroids. If it occurs, the second eye is often affected within 2 weeks; it rarely occurs beyond 2 months [17]. Patients with blindness are also at increased risk of stroke. Bilateral occipitotemporal infarction may occur, resulting in Anton's syndrome, which may explain some reports of blind patients not being particularly concerned about their deficits.

The aetiology of GCA remains unknown. It is known that viruses can induce vasculitic syndromes. Candidate agents in GCA include parvovirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, EBV, RSV, HSV, measles, CMV and parainfluenza virus [18].

Temporal artery biopsy remains the gold standard for the diagnosis of GCA. It helps exclude other arteritides as diagnoses. Beyond this, other arteritides have characteristic presentations. For example, primary angiitis of the CNS has headache as a prominent symptom, but also has multiple strokes and a CSF pleocytosis with a lack of systemic manifestations. Wegener's granulomatosis tends to affect the respiratory tracts and kidneys. Polyarteritis nodosum is also a multisystem arteritis but affects small and medium-sized vessels. The headache of lupus is controversial, but the diagnosis can be made based on serology and clinical presentation [19]. In GCA, the temporal artery biopsy reveals intimal proliferation with luminal stenosis, disruption of the internal elastic lamina by a mononuclear cell infiltrate, invasion and necrosis of the media by mononuclear cells, intravascular thrombosis, and sometimes giant cells with granulomata (not required). Patchy involvement of the arteries leads to the notorious "skip lesions". Three stages of pathologic activity are known: acute/necrotising, granulomatous and regenerative (media fibrosed) [20].

In the pathogenesis of GCA, Th1 lymphocytes recognise antigens which leads to γ interferon (γIFN) production. In turn, macrophages produce interleukin-1 (IL-1, endogenous pyrogen), IL-6, TGFβ, NOS, TNF-α and matrix metalloproteinases (MMP). MMP cause smooth muscle cells to migrate to the vascular lumen. γIFN is crucial for the development of giant cells and granulomata. Giant cells release PDGF and VEGF, which lead to intimal hyperplasia and neoangiogensis [20].

An individual's particular cytokine profile may determine the constitutional symptoms and ischaemia such as fever, weight loss and malaise [21]. IL-6 is a pro-inflammatory cytokine important in the induction of the acute phase response. Interestingly, aspirin suppresses γIFN, while indomethacin does not (and NSAIDs are typically ineffective in GCA) [22, 23]. Therapies for GCA include agents that non-selectively and selectively suppress the immune and vascular responses.

The 1990 Classification of the American College of Rheumatology for GCA are 94% sensitive and 91% specific [24]. They include: age>50, ESR>50, headache of new onset, temporal artery abnormality (tender or Ø pulse), positive temporal artery biopsy. Not all must be present, only three, so the necessity of a temporal artery biopsy has been called into question if other features are present. When considering the diagnosis of GCA, it is prudent to rule out other arteritides, occult infection and malignancy.

Laboratory evaluation in GCA is useful. IL-6 induces the acute phase response so ESR is usually increased, as is C-reactive protein (C-RP). ESR may be normal in 1%–2% of GCA; C-RP may be as sensitive and perhaps more specific [18]. They both tend to be less elevated in occult GCA. Anaemia is seen in 2/3 of patients, leukocytosis in 38%, and abnormal liver chemistries, thrombocytosis and lymphocytosis may also be encountered [25]. ESR normalises with effective therapy, while elevated von Willebrand's factor (due to endothelial dysfunction) and IL-6 remain elevated [18, 20, 25].

Ultrasonography may assist in selecting the site for temporal artery biopsy, demonstrating a hypoechoic halo around the involved lumen [18]. An adequate sample should be taken, with serial sections performed by the pathologist. The false negative rate on bilateral biopsies is probably less than 5%. Ideally therapy with steroids is begun immediately upon suspecting the diagnosis, and the sample should be taken within 1–2 weeks [4]. Positive biopsies have been reported after long periods from the initiation of treatment [26]. Histopathology is not a predictor of clinical outcome [9].

F-18-deoxyglucose PET scanning may show uptake in large thoracic arteries such as the aorta, subclavians or carotids. This is 98% specific for GCA/PMR. However, the sensitivity is only 56% [18]. MRI may show synovitis and bursitis.

In treating GCA, there is no real alternative to corticosteroids. Prednisone, at a dose of approximately 40–80 mg/day, is begun. The dose is gradually reduced following both symptoms and ESR. Symptoms of PMR may appear as the dose is reduced. Relapses are uncommon as long as the prednisone dose is above 7.5 mg/day [4, 9, 18]. Treatment suppresses symptoms but does not shorten the disease duration (IL-6 and von Willebrand's fail to normalise) [18]. GCA is usually a self-limited process, ending after 2–3 years. Alternate day steroids are ineffective, as are NSAIDs [18]. Side effects from therapy are common and include vertebral compression fracture, aseptic necrosis of joints, infection, diabetes mellitus, peptic ulceration, congestive heart failure, cataracts, myopathy and psychosis [27]. GI protective measures, calcium, vitamin D and biphosphonates are usually indicated.

Steroid resistance, implying the need for doses of prednisone >15–20 mg/day beyond 3–6 months after initiation of therapy is seen in perhaps 20% of patients with GCA [20, 28]. For these patients other treatment options need to be considered. Both methotrexate and azathioprine have been advocated albeit with little evidence [18, 20, 25, 29]. Cyclosporine has been ineffective. Dapsone has been abandoned due to serious haematologic side effects [30]. There are also anecdotal reports on hydroxychloroquine, cyclophosphamide and trimethoprim/sulphamethoxazole.

As already stated, the lesions in GCA are driven by Th1 lymphocytes and macrophages and are rich in pro-inflammatory cytokines such as IL-1, TNF-α and γIFN. Because anti-TNF-α therapy in rheumatoid arthritis has been effective, inflixamab (a monoclonal antibody directed against TNF-α) has been reported as a potential treatment in steroid-resistant GCA [31]. Similarly, etanercept (the fusion protein of the extracellular ligand binding portion of the p75 TNF receptor and the Fc portion of IgG1) has been utilised [32]. Interestingly, thalidomide has anti-TNF-α activity, although to date it has not been investigated for this purpose.

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M. Leone • A. Franzini • G. Felisati • E. Mea • M. Curone • V. Tullo • G. Broggi • G. Bussone

Deep brain stimulation and cluster headache

Abstract In recent years, neuroimaging data have greatly improved the knowledge on trigeminal autonomic cephalalgias' (TACs) central mechanisms. Positron emission tomography studies have shown that the *posterior inferior hypothalamic grey matter* is activated during cluster headache attacks as well as in short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). Voxel-based morphometric MRI has also documented alteration in the same area in cluster headache patients. These data suggest that the *cluster headache generator* is located in this region and leads us to hypothesise that stimulation of this brain area could relieve intractable cluster headache just as deep brain stimulation improves intractable movements disorders. This view received support by the observation that high frequency stimulation of the ipsilateral hypothalamus prevented attacks in an otherwise intractable chronic cluster headache patient previously treated unsuccessfully by surgical procedures to the trigeminal nerve. So far, 16 patients with intractable cronic cluster headache (CCH) and one intractable SUNCT patient have been successfully treated by hypothalamic stimulation. The procedures were well tolerated with no significant adverse events. Hypothalamic DBS is an efficacious and safe procedure to relieve otherwise intractable CCH and SUNCT.

Key words Cluster headache • Paroxysmal hemicrania • SUNCT • Therapy • Deep brain stimulation

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Introduction

Trigeminal autonomic cephalalgias (TACs) are a group of primary headache syndromes characterised by two main clinical characteristics: pain and oculofacial autonomic phenomena [1]. Three headache forms are grouped as TACs: cluster headache (CH), paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [1]. These are distinguished mainly on the basis of attack duration. It lasts from 15 to 180 min in CH, from 2 to 30 min in PH and from 5 to 240 s in SUNCT. The most effective preventative drug in PH is indomethacin, although in a few cases other non-steroidal anti-inflammatory drugs have been reported to be effective [2]. SUNCT is commonly described as drug resistant. Recent studies report that lamotrigine may be the drug of choice for SUNCT [3, 4].

In otherwise drug-resistant patients, surgical procedures have to be taken in consideration. Candidates for destructive surgery are chronically intractable cluster patients whose headaches are unilateral with no history of side shift. In patients whose attacks alternate sides, the risk of a contralateral recurrence after surgery is rather high. Various procedures that interrupt either the trigeminal sensory or autonomic (cranial parasympathetic) pathways can be performed although few are associated with long-lasting benefit; in addition side effects can be severely debilitating.

Lack of knowledge on TACs' pathophysiology has hampered development of new therapeutic strategies. In

recent years, neuroimaging data have greatly improved the knowledge on TACs' central mechanisms. Positron emission tomography studies have shown that the *posterior inferior hypothalamic grey matter* is activated during cluster headache attacks [5, 6]. Voxel-based morphometric MRI has also documented alteration in the same area in cluster headache patients [7]. These data suggest that the *cluster headache generator* is located in this region. This view is supported by the observation that high frequency stimulation of the ipsilateral hypothalamus prevented attacks in an otherwise intractable chronic cluster headache patient previously treated unsuccessfully by surgical procedures to the trigeminal nerve [8–10]. A similar activation has been reported also in SUNCT [11].

Deep brain stimulation

By analogy with the use of electrode stimulation for intractable movement disorders it was reasoned that stereotactic stimulation of this area might interfere with this generator and relieve intractable forms of CH [8–10]. The first patient who received hypothalamic stimulation was suffering from severe chronic bilateral intractable cluster headaches; destructive surgery to the left trigeminal was absolutely contraindicated. Electrode implantation and continuous stimulation of the left posterior inferior hypothalamus resolved the left attacks [8, 9]. After four destructive operations on the right trigeminal, right side attacks recurred. Electrode implantation (with continuous stimulation) to the right resulted in immediate resolution of the right side pain. On several occasions, both known and unknown to the patient, the stimulators were turned off: in all cases crises reappeared and all instances disappeared relatively quickly after turning stimulation back on. The only side effects were transient and observed during long-term bilateral stimulation. After 42 months (left) and 31 months (right) of follow-up the patient remains crisis-free without the need for pharmacological prophylaxis [9]. Another 15 patients with intractable CCH have been successfully treated by hypothalamic stimulation [12, 13]. The procedures were well tolerated with no significant adverse events [12]. However, a report on six other intractable CCH patients who underwent hypothalamic electrode implantation showed that the approach is not without dangers: one of the patients died post-operatively following intracerebral haemorrhage [14]. All deep brain electrode implantation procedures are associated with a small risk of mortality due to intracerebral haemorrhage. This kind of procedure can be performed only by a highly experienced neurosurgical group. Activation of ipsilateral hypothalamus has been reported also in SUNCT [11]. Due to inconsistent results of destructive surgery in drug-resistant SUNCT patients, hypothalamic stimulation has been tried in one chronic intractable SUNCT patient. The 11-month follow up shows deep brain stimulation is effective and safe also for SUNCT [15].

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Migraine: barriers for care

Abstract Migraine headaches affect 12% of the adult population in occidental countries and cause a significant economic loss due to decreased workplace productivity. However only a minority of migraine sufferers worldwide ever receive a correct diagnosis or appropriate treatment. Several barriers for adequate care contribute to this situation. In this article we discuss some strategies to bypass these barriers, summarised herein as: (1) identifying migraine sufferers in need of care; (2) improving medical recognition; (3) supporting the differential diagnosis; (4) improving medical confidence; (5) improving medical treatment; and (6) assessing treatment outcomes.

Key words Migraine • Barriers • Recognition • Screeners

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Introduction

Migraine is a frequent, severe, undiagnosed and undertreated disorder with a prevalence of about 12% in occidental countries [1]. In 1999, it was estimated that 28 million Americans suffered from migraine. Besides being prevalent, migraine is often a debilitating neurological disorder. Around 53% of the US migraine sufferers reported that severe headaches caused significant impairment in activities or required bed rest, and 62% reported having severe headaches more than once per month [2]. Migraine ranks within the 20 most debilitating disorders according to a WHO survey [3].

With the recent launch of the joint Global Campaign to reduce the burden of headache by the World Headache Alliance (WHA), the International Headache Society (IHS), the European Headache Federation (EHF) and WHO, a welcome focus on the management of migraine is expected [4]. Migraine management is influenced by numerous factors that are regionally different around the world. A necessary step, however, is the identification and strategies to address barriers for adequate headache care. Herein we briefly summarise some of the already identified barriers.

First barrier: identifying migraine sufferers in need of care

Not all migraine suffers in the society are in need of care. However, those requiring care need to be motivated to enter the health care system. Self-awareness of disease and emphasis on migraine-related disability are necessary steps.

A study investigated whether disability reflects headache severity and the need for medical care [5]. In this study there were significant associations between increasing disability scores and an increasing proportion of indi-

viduals who had consulted a doctor within the past year, lower use of over-the-counter medication, and greater use of prescription medications. Satisfaction with current therapy decreased significantly with increasing disability scores, mirroring the frequency with which individuals achieved complete relief from headache. This study concluded that a low disability score generally seems to indicate a low need for care, while the opposite is true. Therefore, global campaigns should focus first on the awareness of the disease and then on motivating patients who miss or reduce professional or social activities due to their headaches to seek medical care.

Second barrier: improving medical recognition

Less than 50% of the migraine sufferers in the US ever receive a medical diagnosis, and most seek care in the primary care setting [2]. Therefore at this level screening tools may prove useful. Recently two migraine screeners were validated to be used at the primary care level. Lipton et al. [6] developed a three-item questionnaire (asking about nausea, photophobia and disability). In a patient with headache that responds positively to two of the three questions, the positive predictive value for migraine is 93%. Sensitivity was 0.81 (95% CI, 0.77–0.85), and specificity was 0.75 (95% CI, 0.64–0.84) [6].

Cady et al. [7] also developed a three-item migraine screening questionnaire. Questions are: (1) Do you have recurrent headaches that interfere with work, family or social functions? (2) Do your headaches last at least 4 hours? (3) Have you had new or different headaches in the past 6 months? The 3-question headache screen identified migraine in 77% of the study population; including 78% of the patients enrolled based on International Headache Society criteria, 74% based on clinical impression and 68% because of recurring disabling headaches [7].

Third barrier: improving medical diagnosis

Around 42% of migraine sufferers that seek care for headache receive an incorrect sinus headache diagnosis, while 32% receive an incorrect tension-type headache diagnosis [8]. The use of migraine screeners may help to address this barrier, if used together with awareness of migraine programmes.

Awareness programmes should highlight that migraine is by far the most prevalent headache in primary care. Tepper et al. [9] assessed the prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache. A total of 1203 male and female patients between 18 and 65 years of age who consulted their physician with headache as a primary or secondary complaint were included. Overall, 94% of patients with a physician diagnosis of nonmigraine primary headache or a new clinic diagnosis of migraine had IHS-defined migraine (76%) or probable migraine (migrainous) (18%) headache on the basis of longitudinal diary data. A new clinical diagnosis of migraine was almost always correct: 98% of patients with a clinical diagnosis of migraine had IHS-defined migraine (87% of patients) or probable migraine (11% of patients) headache on the basis of longitudinal diary data. On the other hand, review of diaries of patients with a clinical diagnosis of nonmigraine revealed that 82% of these patients had IHS-defined migraine (48%) or probable migraine (34%) headache. Altogether, one in four patients (25%) with IHS-defined migraine according to longitudinal diary data did not receive a clinical diagnosis of migraine. These findings support the diagnostic approach of considering episodic, disabling primary headaches with an otherwise normal physical exam to be migraine in the absence of contradictory evidence. If in doubt of diagnosis or when assigning a nonmigraine diagnosis, strong consideration should be given to the use of a diary to confirm primary headache diagnosis.

Fourth barrier: improving medical confidence

Migraine sufferers more often seek care at the primary care level. Primary care doctors are often afraid of missing secondary headache disorders, or are unconfident with a migraine diagnosis. The consequences include unnecessary referrals to neurologists, as well as unnecessary neurodiagnostic investigation.

The Headache Consortium Guidelines recommend that a patient should be investigated if red flags are found during the anamnesis and physical exam. Red flags have been described elsewhere. In a patient with migraine, no red flags and normal physical exam, the probability of *significant* intracranial pathology is only 0.18% [10].

Fifth barrier: improving migraine treatment

Data from the American Migraine Study II show that just 41% of migraine sufferers in the US ever received a prescription for migraine and 6 out of 10 sufferers (59%) are still relying on OTC medication or no medication to manage headache pain [2]. This problem is not restricted to the US. A recent large Latin American study showed that the agents used most widely to treat migraine were paracetamol and salicylates. Medication use varied widely among countries, but was predominantly nonprescription. Triptans and preventive drugs were very infrequently prescribed [11].

Headache guidelines certainly play a role here. Disability and outcome tools may also play a role as well. The Headache Consortium Guideline clearly states that triptans should be used in migraine sufferers with disability (the vast majority of those who seek care) unless contraindicated. Additionally, although guidelines vary, it is consensual that prevention should be used in those with 8 or more days of migraine per month, or less than 8 days but disabled even after using appropriate acute therapies.

Sixth barrier: assessing treatment outcomes

Several drugs from different classes are approved for the acute and preventive treatment of migraine. For ongoing assessment, we need to define treatment goals and, to some extent, the goal of migraine therapy to relieve pain, restore the ability to function, and to do that safely and with minimal side effects. However, the way various aspects of treatment get prioritised across individual patients really varies, and it is, therefore, necessary to individualise treatment goals and to assess treatment *vs*. those goals. Again, employing disability tools may be useful as a way of following the progress that patients are making.

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Pharmacogenetics of headache treatment

Abstract Headaches and migraines are widely prevalent diseases causing relevant disability and worsened quality of life. Several pharmacological options are available for headache therapy, mostly however without firm rationales and all having high rates of non-responders and often serious side effects. Variability of therapeutic effect and adverse events depend at least in part upon genetic variability, but the genetic factors involved are mostly unknown. Pharmacogenetics, i.e., the application of the knowledge of genomic diversity to the analysis of the phenotypic traits involved in therapeutic response and adverse events, is still in its infancy, but represents a promising approach to therapy in migraine. The extant evidence is summarised here, with special attention to pain therapy and the pharmacogenetics of the serotonergic and the dopaminergic systems.

Key words Pharmacogenetics • Pharmacogenomics • Migraine • Headache

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Introduction

Pharmacogenetics is the discipline applying knowledge of genetic diversity to the prediction of drug response. Pharmacogenetics is based on the analysis of all possible genetic variations capable of influencing the activity of any one specific drug. While pharmacogenomics is a term best reserved for drug discovery and development derived from such genetic knowledge, the two terms are often used interchangeably. Pharmacogenetics has been around for several decades, but has really been developing as a revolutionary discipline in recent times. The advances in molecular genetics and the completion of the Human Genome Project have given impetus to pharmacogenetics and even afforded the promise of individualised drug therapy. While such promise may seem overstated at the present time, other aspects of pharmacogenetics, in particular the possibility of predicting individual or ethnic groups adverse events and thus of substantially impacting pharmaco-surveillance represents realistic and significant advances. Indeed, well known and easily quotable instances of the importance of pharmacogenetic surveillance are those disease entities entirely dependent on the use (or abuse) of drugs, such as malignant hyperthermia and the hepatic porphyrias.

Pharmacogenetics: general considerations

It is every day's and every physician's experience that responses to drugs differ from one individual to the other. Drug levels can vary even more than 1000-fold in individuals given the same dose and having the same weight. Phenotypic variation has been considered to account for 50% of adverse drug reactions encountered in the clinical setting; here, more than half of the drugs involved were metabolised by enzymes with variants causing poor

metabolism [1]. Genetic diversity is therefore all important here, individual variability to the effects of treatments being underscored by variant polymorphisms in genes. Genetic polymorphisms often vary not only among different individuals but also in ethnic groups. Specific differences in genes relevant to their function (functional polymorphisms) are able to modify important biochemical properties of endogenous proteins and enzymes that regulate metabolism (pharmacokinetic profile) and mechanisms of action (pharmacodynamic properties) of drugs. Drugs are molecules that exert their effect by the action of the active metabolite(s) on a target endogenous protein, either represented by an *enzyme*, catalysing a biochemical reaction, or a *receptor protein*, whereby binding to it by the active metabolite mediates (activates or inhibits) a specific reaction. Single genes involved in the metabolism of drugs (such as the drug-metabolising cytochrome-P450 enzymes, the acetyl-, methyl- and glucuronyl-transferases etc), drug transporters and other trans-membrane target proteins, and ion channels usually show wide genetic variety with several genetic polymorphisms and sometimes even genetic mutations having different functional properties. Already, over 4 000 000 inter- and intra-gene human polymorphisms have been characterised, many of them displaying functional activity. Such staggering numbers allow a glimpse of the extreme variability of the human genome and of the enormous problems connected with the pharmacogenetics of any particular drug in any particular individual, especially when we consider that drug responses are as a rule multifactorial, i.e., depend on the action of several genes interacting with several environmental factors.

In the experimental setting, any pharmacogenetic analysis needs to start with the analysis of genetic variation, and thus employs the tools needed for genotyping. Phenotypes (such as for instance the levels of activity of enzymes involved in drug metabolism) must be previously defined, and this is usually attained by administering appropriate pharmacological probes testing the different metabolic pathways. Any phenotypic expression (phenotypic trait) is then analysed against the genotypic set. Pharmacogenetic phenotypes are usually polygenic and multifactorial and, in particular when dealing with the clinical effects of drugs, graded responses should be expected. In the setting of clinical trials too, pharmacogenetics start with the dissection of phenotypic heterogeneity, and specifically the isolation of those patient populations in a clinical trial more or hyper-responsive to the drug or, conversely, displaying significant adverse effects. Such clinical phenotypes are then "measured" against the corresponding genotypic sets, allowing the discovery of the genetic polymorphisms involved in the therapeutic response or its adverse effects. Relevant clinical therapeutic and commercial implications can be expected from such approaches in the near future.

Genetics of primary headaches

Among the primary headaches, migraine is generally conceived as a multifactorial disease. Only a variety of migraine with aura, familial hemiplegic migraine (FHM), conforms to a simple mendelian type of hereditary transmission, and indeed two genes have been discovered responsible for FHM1 and FHM2, *CACNA1A* and *ATP1A2*. Their relevance to the more common forms of migraine is however disputed. Several association and linkage studies are available for the typical migraines (with and without aura). In view of the treatment options available in migraine, the studies most relevant here seem to be those analysing the role of genetic variations in genes involved in the metabolism of dopamine and serotonin, catecholamines both thought to underlie at least part of the mechanisms of migraine. It is impossible to detail these studies here. Tables 1 and 2 summarise the genetic association and linkage studies exploring dopaminergic and serotonergic metabolism genes. Remarkably, headache genetics has paid no great attention for genes involved in nociception.

Treatment and pharmacogenetics of headache

Treatment of migraine develops along several therapeutic strategies, mostly based on empirical rationales. A distinction is usually drawn between acute treatment of the migraine attacks, and prophylactic treatments, aimed at those patients with a high severity and frequency of the attacks. Several drugs used for the treatment of the attacks are unspecific, and happen to be used in the treatment of other painful acute conditions. They are analgesics such as paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs: aspirin, naproxen), etc. Analgesics and NSAIDs may be combined with antiemetics (metoclopramide) and with caffeine. A more specific drug for acute migraine treatment is ergotamine, an ergot alkaloid with potent vasoconstrictor activity. In recent years seminal advances in migraine therapeutics were afforded by the development of the triptans, drugs tailored to interact selectively with 5-HT receptors in cranial blood vessels. Triptans mediate vasoconstriction of meningeal vessels via stimulation of vascular 5-HT1B receptors, inhibit neurogenic inflammation by stimulation of presynaptic 5-HT1D-1F receptors and, possibly, also inhibit central pain pathways.

Prophylactic treatment of migraine involves the use of beta-adrenoceptor antagonists like propranolol, calcium channel blockers, or tricyclic antidepressants and 5-HT antagonists, f.i. methysergide. As evident from the range of pharmacological options, the modes of action in prophylactic treatment of migraine are mostly unknown,

reflecting our ignorance of the pathogenic mechanisms of the disease. Furthermore, even the highly efficacious triptans have shortcomings, such as recurrence of headache after initial relief and a rate of non-responders of at least 15%. About 40% report chest-related symptoms and other adverse events. Myocardial infarction and cardiac arrest have also been reported. These individual differences in response and adverse effects remain unexplained. However, some precursory studies were done in this regard by MaassenVanDenBrink et al. [2], who investigated the allele frequencies of two polymorphisms in the 5-HT1B receptor gene (G861C and T-261G) in migraine patients either with consistently good response to sumatriptan (14), with no response (12), with recurrence of the headache (12), and with (13) and without chest symptoms (27). Allele frequencies (G:0.74; C:0.26 at nt 861 and T:0.39; G:0.61 at nt -261) did not differ between patient groups, thus indicating that genetic diversity at the 5-HT1B receptor was not responsible for the different clinical responses to sumatriptan. In another study on the same population [3], they investigated the chromosomal localisation of the 5-HT1F receptor gene and the relation between eventually existing polymorphisms and the clinical response to sumatriptan. The 5-HT1F receptor gene was localised at 3p12, but no polymorphisms could be detected. Again, genetic variability at the 5-HT1F receptor gene could not account for the variable clinical response to sumatriptan. Other polymorphisms in 5-HT receptor genes are known (F124C for 5-HT1B, and C23S for 5-HT2C) which affect the binding of dihydroergotamine, sumatriptan and serotonin [4, 5], but none of them has yet been studied in migraine patients until now.

Pharmacogenetics of the dopaminergic and serotonergic systems

These pharmacological systems are relevant to the pathogenesis of migraine, as some symptoms occurring at the onset of the migraine attacks (nausea, vomiting, yawning) are mediated by the dopamine system, and serotonin abnormalities have been established in migraine. Moreover, there is genetic evidence, albeit controversial, for the involvement of dopamine and serotonin metabolism genes in the genetics of the primary headaches (see

Table 1 Linkage and association studies of genes regulating serotonin metabolism in migraine

Gene (s) studied	Phenotype (MA: migraine with aura; MO: migraine without aura) (authors)
5-HTSERT (17q11.2-12)	Allelic association with MO (increased STin2.12+decreased STin2.10 alleles) and MA (idem+increased Stin2.9 alleles) (Ogilvie et al., 1998) Allelic association with migraine (increased Stin2.10 allele!) (Ylmaz et al., 2001) Borderline association with migraine (Juhasz et al., 2003) No association or linkage with migraine (Monari et al., 1997; Lea et al., 2000)
5-HT2A (13q14-21)	Allelic association (C allele) with aura but not with migraine (Erdal et al., 2001) No association or linkage with migraine (Monari et al., 1997; Nyholt et al., 1996; Buchwalder et al., 1996; Juhasz et al., 2003)
5-HT1B (6q13), 5-HT1D (1p36.3-34.3), 5-HT2B (2q36.3-q37.1), 5-HT2C (Xq22-25)	No association or linkage with migraine (Monari et al., 1997; Buchwalder et al., 1996; Burnet et al., 1997; Johnson et al., 2003)
5-HT1B (6q13), 5-HT1F (3p12)	Not associated with therapeutic response to triptans (VanDenBrink et al., 1998; 1998).

Table 2 Linkage and association studies of genes regulating dopamine metabolism in migraine

Gene(s) studied	Phenotype (MA: migraine with aura; MO: migraine without aura) (authors)
DAT (dopamine transporter)	Associated with chronic migraine with drug abuse (Mochi et al., 2003)
DRD2 (dopamine receptor 2)	Allelic association (NcoI allele) with MA (Peroutka et al., 1997) Allelic association (NcoI allele) with MA co-morbid with anxiety/depression (Peroutka et al., 1998) Allelic association (allele 1) with yawning/nausea during the MO attack (Del Zompo et al., 1998) No allelic (NcoI allele) association with MA (Dichgans et al., 1998) No allelic association with MO/MA (Mochi et al., 2000) No allelic association with migraine (Lea et al., 2000)
DRD1, DRD3, DRD4, DRD5 COMT, MAO-A	No association with migraine (Del Zompo et al., 1998; Mochi et al., 2000, Shepherd et al., 2002) DRD4 associated with MO (Mochi et al., 2003)
DBH (dopamine-beta-hydroxylase)	Allelic association with typical migraine (Lea et al., 2000) No association with migraine (Mochi et al., 2003).

Tables 1 and 2). Antidepressants and other drugs (methysergide) acting on the serotonin metabolism and antidopaminergic agents such as metoclopramide represent useful therapeutic options in migraine. Interestingly, the serotonin transporter (5-HTSERT) reuptakes serotonin at the synaptic terminal and constitutes the principal mechanism eliminating serotonin from the synaptic cleft. The 5-HTSERT is the target of the SSRI antidepressants. Its gene has two alleles, a long (16 copies of a 20–23 base pair repeat unit) and a short one (14 copies), with different functional properties. The presence of at least one copy of the long allele seems associated with a favourable response to the SSRIs [6, 7]. As for the efficacy of neuroleptics, Arranz et al. [8] showed an association between 5-HT2A receptor polymorphisms (T102C and His452Tyr) and response to the atypical neuroleptic clozapine. A 77% predictability of the clinical effects of clozapine was afforded by a combination of six polymorphisms involving several receptors [9]. Furthermore, a significant side effect of clozapine, agranulocytosis, is associated with the major histocompatibility complex region HSP70-1 and -2 [10], while dyskinesia is associated with the Ser9Gly polymorphism of the dopamine receptor DR3 gene [11].

Pharmacogenetics of addiction

Addiction, defined as a compulsive search and assumption of drugs and substances despite recognised undesirable effects, can in principle be attributed either to the effects of a toxic substance intake modifying the functionality of the brain and leading to a state of dependency; or to a pathological interaction of an individual genetic susceptibility trait with the toxic substance. From a neurobiological point of view, the process of reward, the final pathways to drug intake and probably drug abuse, is especially dependent upon the dopaminergic system and dopaminergic activation. Twin studies and genetic association studies of the dopaminergic and serotonergic systems have been dedicated to drug addiction and have confirmed the role of genetic factors in the development of substance addiction. Thus, genetic predisposition to drug abuse has been traced to polymorphisms in genes, such as the dopamine receptor DRD4, allele 9 of the dopamine transporter (DAT) gene and the catechol-ortho-methyl-transferase (COMT) and mono-amino-oxidase A (MAOA) genes, regulating dopaminergic transmission.

Headache pain may recur daily or near daily, giving rise to the so-called chronic daily headache (CDH), a relevant source of pain and disability with difficult treatment options [12]. CDH carries a genetic predisposition [13] and is often associated with drug abuse [14] and with psychological and personality traits predisposing to chronicisation of pain [15] and also to abuse of analgesics. CDH with drug abuse represents a serious source of pain and adverse effects and is a widely prevalent and often under-recognised disease, reaching prevalence rates of 2%–8% among the general population. CDH with drug abuse has been conceived by some authors as an addictive disease, in which drug intake is conducive to chronicisation of migraine. Pharmacogenetic studies are not available in the CDH. However in a study of the genetic liability to CDH with drug abuse, a genetic association study of functional polymorphisms of the DRD4, DAT, MAOA and COMT genes, all involved in dopamine metabolism, showed that allele 10 of the DAT gene was significantly under-represented in patients with CDH and drug abuse when compared to the episodic headache patients. This suggested that liability to drug abuse in chronic headache involves genetic variability at the DAT gene [16]. These findings may offer a rationale for pharmacologic manipulation of the dopamine system in the CDH with drug abuse.

Conclusions

Pharmacogenetics of headache and migraine is still in its infancy: the causes of the wide variability in therapeutic effects and adverse events of the various antimigraine drugs remain completely unexplained. We may expect and must wait for future advances in the genetics of migraine and other headaches that will offer better rationales for scientific enquiry, thus helping the discovery of new treatment pathways for headache pain and lowering the ever relevant rates of non-responders to the actual therapeutic armamentarium. Advances in the genetics of pain and pain treatment are even more likely to relevant for headache, allowing at least explanations for unwanted side effects and the lack of therapeutic response. These advances will then be measured against their socio-economic implications, with their advantages and costs to the individual patient and the health system.

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ORAL COMMUNICATION

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Frequency of headaches in patients over 80. A preliminary report

Abstract We evaluated 44 old patients (mean age 84 years) in order to study the frequency of hedaches. The frequency found in our sample is higher in comparison to other studies. Further studies including a larger number of patients are needed to obtain more incisive results.

Key words Headaches • Elderly patients • Frequency

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Introduction

Although headache is one of the most frequent complaints in elderly people [1], data in this segment of the population are sparse because samples examined lack patients over 65 years or their number was not large enough [2–10].

We evaluated 44 very old patients, living in home hospice, to study the type and the frequency of headaches.

Material and methods

We enrolled in the study 44 old persons (42 female and 2 male), with mean age 84 (range 79–97). All patients were submitted a questionnaire, based on IHS criteria [11], for the diagnosis of headaches. All patients were screened with the Mini-Mental State Examination (MMSE) before the administration of the IHS questionnaire: they were enrolled if MMSE was >24.

Results

We found 8/44 patients (18%) (all patients were female) suffering for primary headaches. Four patients (9%) suffered for migraine, 1 (2.2%) probable migraine (PM), 2 (4.5%) tension-type headache (TTH) and one patient (2.2%) complained of probable tension-type headache (PTTH). The mean age was 87.65 years, *vs*. 85 years for subjects without headache. All sufferers were female, and the age of onset of pain was under 30 years in 5 patients, whereas it was over 70 in the remaining 3. None of them complained of worsening of pain or increase of frequency in the last year; intensity was moderate in 3, severe in 1 and low in the patient with PM. The patients with TTH complained of low (1 patient) and moderate pain (1 patient), whereas the patient with PTTH showed moderate pain.

In all patients except one, vegetative symptoms (nausea and vomiting) were absent.

The type of pain was dull in 6 patients, and throbbing in 2 patients suffering for migraine. The duration of pain was over 4 hours in all migraineurs and in 1 patient with TTH. Physical activity worsened the intensity of pain in all patients except two, both sufferers of TTH. Finally the intensity of pain was low in two subjects, with PM and TTH.

Discussion

The data of the frequency of headaches in older people are inconclusive in the literature, for the different characteristics of samples evaluated.

Frequently, in the samples examined, elderly patients (over 80) were rare and, when present in the examination, a different methodology was utilised.

Frequently, 1-year prevalence has been evaluated. Although this is a very careful method, it is probably not representative of migraine, a chronic disease with a life course. Some authors utilised telephone interviews, others mail interviews and others door-to-door surveys.

We have studied elderly patients living in a home care institute: this could have restricted the criteria of patient choice but is the only way to study patients of such advanced age.

Our samples are scant, and males are completely absent (this is probably because women live longer than men).

In our group the frequency of migraine is higher in comparison to other studies cited in specific literature. This finding may be related to the small number of patients evaluated.

Our data may be in agreement with the hypothesis that primary headaches (not only TTH) are probably more frequent than previously reported, also in elderly patients. Many more patients are needed to obtain more incisive results.

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ORAL COMMUNICATION

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A clinical comparison of trigeminal neuralgic pain in patients with and without underlying multiple sclerosis

Abstract Despite clinical similitude, there is a tendency to consider trigeminal pain in multiple sclerosis (MS) as a distinct condition. To evaluate clinical differences in trigeminal pain presentation in patients with and without underlying MS, we compared clinical characteristics of facial pain found in 15 consecutive MS patients with those reported by 13 consecutive subjects diagnosed with classical trigeminal neuralgia. The only significant difference between MS and non-MS neuralgic patients was the age of onset of pain (43.4±10.5 in MS *vs.* 59.6±11.50 in non-MS patients, p=0.000629, unpaired Student's t-test). No differences were observed for side, duration and quality of pain, trigeminal branches involved, presence of trigger areas or factors, pain refractive period, remitting-relapsing or chronic course. There was only a trend without statistical significance in interval pain and trigeminal hypoesthesia, more frequent in MS population. Only one patient in the MS group presented with long-lasting episodes (45–60 min) of atypical odontalgia. Our findings support the view of a common pathogenetic mechanism underlying TN in the two groups, possibly related to demyelination of the trigeminal entry root in the pons. Typical TN in MS patients should be considered as "symptomatic trigeminal neuralgia".

Key words Trigeminal neuralgia • Multiple sclerosis • Facial pain • Symptomatic

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Background

The prevalence of trigeminal neuralgia (TN) is higher (2%) in multiple sclerosis (MS) [1] as compared to the prevalence in the general population (15/100 000) [2]. Despite clinical similitude, there is a tendency to consider trigeminal pain in MS patients as a distinct condition, resulting in the recent proposal by the International Headache Society [3] of a new headache subtype, "*13.18.3 Facial pain attributed to multiple sclerosis*", with a separate set of diagnostic criteria.

To evaluate clinical differences in trigeminal pain presentation in patients with and without underlying MS, we compared clinical characteristics of facial pain found in a group of MS patients with those reported by a group with classical TN.

Methods

Clinical characteristics of facial pain reported by 15 MS patients consecutively observed at the day-hospital of our Neurological Institute were compared with corresponding data of 13 consecutive patients attending the Headache Centre of the same department, diagnosed as "*13.1.1 Classical trigeminal neuralgia*" according to the ICDH-2 criteria [3]. All data were collected by a single neurologist with experience in headache and facial pain, using a computerised semi-structured interview [4].

Results

The only significant difference between MS and non-MS neuralgic patients was the age of onset of pain (43.4±10.5 in MS *vs.* 59.6±11.50 in non-MS patients, p=0.000629, unpaired Student's t-test). No differences were observed for side, duration and quality of pain, trigeminal branches involved, presence of trigger areas or factors, pain refractive period, remitting-relapsing or chronic course (for more details see Table 1). There was only a trend without statistical significance in interval pain and trigeminal hypoaesthesia, more frequent in MS

Table 1 Comparison of clinical characteristics of trigeminal pain in MS patients *vs*. non-MS patients. Data are expressed as n (%) if not otherwise indicated

	MS+ (n=15)	MS- (n=13)	*p*
Age of onset, mean±SD	43.4±10.5	59.6±11.5	0.000629
Side			
Left	6 (40.0%)	4 (30.7%)	n.s.
Right	9 (60.0%)	9 (69.2%)	
Pain duration			
<1 s up to 2 min	14 (93.3%)	12 (92.3%)	n.s.
Pain quality			
Superficial and stereotyped	14 (93.3%)	13 (100%)	n.s.
Trigeminal branches involved (alone or in combination)			
I	3/23 (13.6%)	8/25 (32.0%)	n.s.
II	10/23 (43.47%)	10/25 (40.0%)	
III	10/23 (43.47%)	7/25 (28.0%)	
Trigger areas/factors	14 (93.3%)	12 (92.3%)	n.s.
Pain refractive period	6 (40.0%)	6 (46.1%)	n.s.
Periodicity of pain			
Remitting-relapsing	10 (66.7%)	8 (61.5%)	n.s.
Primary chronic	3 (20.0%)	2 (15.4%)	
Secondary chronic	2 (13.3%)	3 (23.1%)	
Trigeminal hypoaesthesia	10 (66.6%)	4 (30.7%)	n.s.
Interval pain	6 (40.0%)	3 (23.0%)	n.s.

patients. Only one patient in the MS group presented with long-lasting episodes (45–60 min) of atypical odontalgia, extended to extra-trigeminal areas.

Discussion

Our data indicate that differences in trigeminal pain characteristics between MS and non-MS patients are limited to the age of onset, while no differences in other variables can be detected. These findings support the view of a common pathogenetic mechanism underlying TN in the two groups, possibly related to demyelination of the trigeminal entry root in the pons [5, 6]. In our series 14 out of 15 MS patients with facial pain shared the clinical features of symptomatic TN. Typical TN in MS patients should be considered as "*13.1.2 Symptomatic trigeminal neuralgia*", reserving for MS patients with atypical facial pain the diagnosis of "*13.18.3 Facial pain attributed to multiple sclerosis*".

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ORAL COMMUNICATION

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Effects of amitriptyline and intra-oral device appliance on clinical and laser-evoked potentials features in chronic tension-type headache

Abstract In the present study, we examined clinical and laser-evoked potentials (LEP) features in two groups of chronic tension-type headache (CTTH) patients treated with two different approaches: intra-oral appliance of prosthesis, aiming to reduce muscular tenderness, and 10 mg daily amitriptyline. Eighteen patients suffering from CTTH (IHS, 2004) participated in the study. We performed a basal evaluation of clinical features and LEPs in all patients (T0) *vs*. 12 age- and sex-matched controls; successively, patients were randomly assigned to a two-month treatment by amitriptyline or intra-oral device appliance. The later LEPs, especially the P2 component, were significantly increased in amplitude in the CTTH group. Both the intra-oral prosthesis and amitriptyline significantly reduced headache frequency. Total Tenderness Score was significantly reduced in the group treated by the prosthesis. The amplitude of P2 response elicited by stimulation of pericranial zones showed a reduction after amitriptyline treatment. The results of this study may confirm that pericranial tenderness is primarily a phenomenon initiating a self-perpetuating circuit, favoured by central sensitisation at the level of the cortical nociceptive areas devoted to the attentive and emotive compounds of pain. Both the interventions at the peripheral and central levels may interrupt this reverberating circuit, improving the outcome of headache.

Key words Tension-type headache • Laser-evoked potentials oral prosthesis

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Introduction

Although tension-type headache (TTH) is the most common type of primary headache, there is little knowledge of its pathophysiology. In a recent study we examined features of laser-evoked potentials (LEPs) [1], as well as cutaneous heat-pain thresholds to laser stimulation, in relation to the tenderness of pericranial muscles in chronic TTH (CTTH), during a pain-free phase [2]. The amplitude of the N2Aa–P2 complex elicited by stimulation of the pericranial zone was greater in TTH patients than in controls; the amplitude increase was significantly associated with the Total Tenderness Score (TTS). Our findings suggested that pericranial tenderness may be a primary phenomenon that precedes headache, and it should be mediated by greater pain-specific hyper-vigilance at the cortical level. Multichannel recording of LEPs allows a topographic analysis to be performed and allows examination of all the LEPs' components; the earlier ones originating from the suprasylvian region (parietal operculum, SII), mainly devoted to the discriminative component of pain, and the later from the anterior cingulate cortex [3], subtending the attentive and emotive features of pain.

The first aim of the present study was to extend previous analysis of LEPs in CTTH, performing a multichannel

topographic analysis during the pain-free phase in comparison to a group of normal subjects, also correlating the LEP findings with the TTS, the main clinical features and the levels of anxiety and depression scored by the Zung (1965, 1976) scales [4, 5].

The second aim of the study was to examine the effect of a specific intervention at the peripheral level consisting of an intra-oral appliance device, *vs*. the central-acting treatment by amitriptyline, on the LEPs, the TTS and the main clinical features of two groups of CTTH patients.

Methods

Eighteen outpatients attending the Headache Centre of the Neurology Clinic of Bari University, who fulfilled the criteria of CTTH associated with pericranial muscles tenderness, according to International Headache Society (IHS) (code 2.3.1) [6], participated in the study. Twelve gender- and age-matched controls were selected, each without any history of headache or other cranio-facial pain according to IHS criteria. All patients who participated were instructed to come to the recording session free from pain and free of medication intake for at least the last 12 h.

All subjects underwent a recording session with 23 scalp electrodes, placed according to the 10–20 International System. The stimulus was a laser pulse generated by CO_2 laser; the dorsum of the hand and the cutaneous zones corresponding to pericranial muscles were stimulated. We performed a basal evaluation of LEPs, clinical features and TTS in all patients (T0); after this one patient was randomly allocated to the amitriptyline group for one who entered the intra-oral device group. It was an open-label randomised study. Patients assigned to the drug therapy took 10 mg amitriptyline daily in the evening. In the other group, a specially designed prosthesis, aiming to reduce pericranial tenderness, was applied, which was prepared at the Johannesburg Headache Clinic on the basis of previous experience of myofascial pain and headache (Fig. 1). The clinical and LEP evaluations were performed in basal conditions (T0) and after two months treatment (T1).

Results

Clinical features

The mean TTS was significantly higher in patients than controls (F=33.5, p<0.0001). The SAS and the SDS scores were also significantly different between the two groups (SAS: F=9.51, p<0.005; SDS: F=24.21, p<0.0001).

LEPs

The temporal N1 amplitude was not significantly different between patients and controls, for any of the sites of stimulation; the amplitude of the vertex N2A was significantly different when all the stimulation points, except for the temporal site, were considered; the vertex P2 amplitude significantly differentiated patients from controls when all the pericranial points were stimulated.

Effects of treatment

Clinical features

Both the oral appliance and amitriptyline significantly reduced the frequency of headache: the two-way ANOVA,

Fig. 1 An example of an oral prosthesis. The final shape and thickness were of course different for each patient

with the treatment and the condition as factors, showed a significant effect of the treatment (F=56.5, p<0.0001), which was not dissimilar between the two groups (treatment x condition: F=0.4, p=0.53). The TTS was significantly different between the two groups, for reduced values in the group treated by the prosthesis (ANOVA with treatment as factor F=17.11, p=0.0001).

LEPs

The amitriptyline provoked a reduction of the vertex P2 at the neck point, masseter and temporal sites. The oral device did not reduce the amplitude of LEPs at any stimulated point.

Conclusions

Taken together, the results of this study may confirm that pericranial tenderness seems to be a primary phenomenon in CTTH. It was correlated with a great activation of the cortical nociceptive areas subtending the emotions and the attention against pericranial painful stimuli. According to the Bendtsen hypothesis [7], pericranial tenderness may initiate a self-perpetuating circuit in which the prolonged nociceptive inputs from pericranial myofascial tissues cause central sensitisation at the level of the spinal dorsal horn/trigeminal nucleus, with supraspinal sensitisation and great activation of cortical nociceptive areas, which contribute to increase the pericranial muscle activity and the painful afferent stimuli. Though our therapeutic design was not exhaustive for the lack of placebo control, it may be suggested that intervention at both the peripheral and central levels may interrupt this reverberating circuit, improving the outcome of headache.

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ORAL COMMUNICATION

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Thunderclap headache caused by spontaneous intracranial hypotension

Abstract We report a group of 4 patients with thunderclap headache as the initial manifestation of spontaneous intracranial hypotension.

Key words Thunderclap headache • Orthostatic headache • Spontaneous intracranial hypotension • Meningeal enhancement

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Introduction

An excruciating headache of instantaneous onset is known as a thunderclap headache (TH). A subarachnoid haemorrhage (SAH) is the prototypical cause, but other serious disorders may also present with a TH, including cerebral venous sinus thrombosis, carotid artery dissection and pituitary apoplexy. We report on 4 patients with TH as the initial manifestation of spontaneous intracranial hypotension (SIH).

Materials and methods

In the period 1992–2004, we observed 24 patients affected by SIH. One patient was affected by Marfan's syndrome. The diagnosis of SIH was confirmed by brain magnetic resonance imaging (MRI) in all patients.

Results

Among the group of 24 patients, four (16%) had experienced an excruciating headache of instantaneous onset (Table 1). The mean age of these three women and 1 man was 31 years (range, 24–45 years). Excruciating pain duration range was 10 seconds to a few minutes. The pain suffered was described as head swelling or as a hard stroke on the head, followed by gravative occipito-nuchal and frontal orthostatic headache. The delay between the onset of headache and diagnosis of SIH ranged from 9 days to 1 month. Mild neck stiffness was present in 2 patients. SIH was clearly demonstrated on brain MRI (Fig 1). Spinal MRI and MRI myelography (3 patients) did not show cerebrospinal fluid (CSF) leak level. Radioisotope cisternography (RC) (2 patients) showed indirect signs of CSF leak. Only in 1 patient was CSF leak demonstrated with CT myelogram at cervical level (Fig. 2). Opening CSF pressure was low (3 patients). CT scan, cere-

Table 1 Characteristics of four patients with TH and SIH

Patient no.	Age, years/sex	Headache	Associated symptoms	Neurological examination findings	MRI findings	Lumbar puncture findings	Location of CSF leak
1 RM	43/F	Acute, severe, occipital, nuchal	Nausea, vomiting, diplopia	Normal	Meningeal enhancement, brain sagging	OP: unmeasurable	Unidentified
2 DR	26/F	Acute, severe, occipital	Nausea, diplopia	Mild nuchal rigidity	Meningeal enhancement, subdural collection	OP: unmeasurable	Unidentified
3 SR	25/M	Acute, severe, generalized	Nausea, vomiting	Normal	Meningeal enhancement	Not performed (patient treated with warfarin)	Probable at sacral meningeal diverticula
4 MP	31/F	Acute, severe, occipital, nuchal	Nausea, vomiting	Mild nuchal rigidity	Meningeal enhancement	OP: unmeasurable	Cervical

CSF, cerebrospinal fluid; *MRI*, magnetic resonance imaging; *OP*, opening pressure

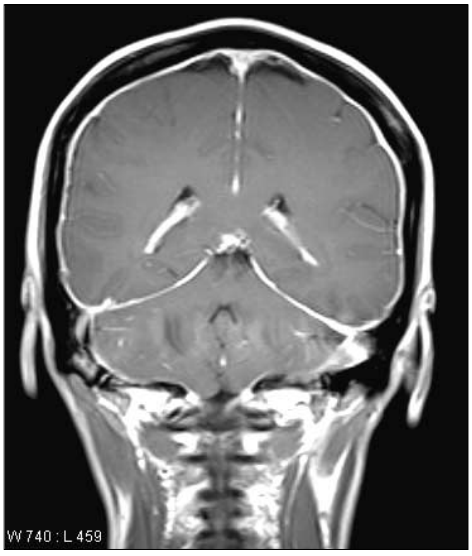

Fig. 1 Patient 4. Coronal T1-weighted gadolinium-enhanced MRI shows diffuse pachymeningeal enhancement

bral angiography (1 patient) and MRI angiography (1 patient) were normal.

Three patients received supportive measures only (bed rest, analgesic and hydration); one patient with cervical CSF leak underwent epidural blood patch.

Discussion

SIH is increasingly recognised as a cause of postural headaches [1]. The diagnosis is made by lumbar puncture revealing low opening CSF pressure, diffuse pachymeningeal enhancement or brain sagging on MRI, or the demonstration of a spinal CSF leak on CT myelography, RC, or spinal MRI or MRI myelography.

Treatment may include bed rest, epidural blood patching or surgical repair of the CSF leak [2].

SIH was initially mistaken for an SAH in these patients. Headache was severe and instantaneous in onset

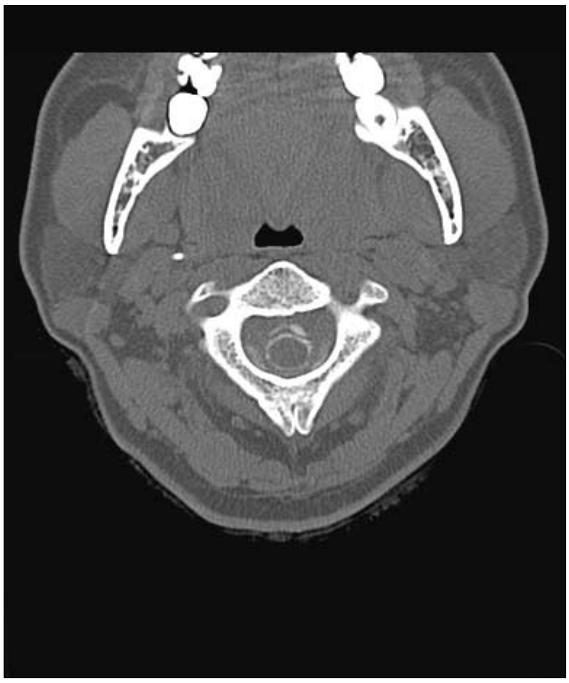

Fig. 2 Patient 4. CT myelogram of the cervical spine shows extrathecal contrast

but nuchal rigidity was found in 2 patients. Meningeal irritation is a cardinal feature common to both SIH and SAH. Other clinical features include the common occurrence of physical exertion preceding the onset of headache, such as sexual or sporting activities, and an association with generalised connective tissue disorders [3].

Additional potential pitfalls in patients with SIH are related to the frequent occurrence of cranial nerves dysfunction.

To further complicate the diagnosis, CSF examination in SIH sometimes may reveal xanthochromia. In addition, because of the very low opening pressure, a traumatic bloody tap is common in patients with SIH. Careful measurement of opening pressure is useful for diagnosis.

The instantaneous onset of headache in the patients described here is likely to have occurred at the time that the leak first developed, probably because of a great CSF leak through spinal dural hole.

We suggest that SIH should be included in the differential diagnosis of TH even when meningismus is present.

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ORAL COMMUNICATION

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Ear acupuncture in the control of migraine pain: selecting the right acupoints by the "needle-contact test"

Abstract There is increasing evidence that somatic acupuncture can be helpful in migraine treatment, but substantial data on ear acupuncture (EAP) are still lacking. EAP can be useful both in the diagnosis and in the treatment of many medical conditions. As regards the control of migrainous pain, we present a case report in which a procedure called the "needle-contact test" is described in detail. During a migraine attack, the patient undergoes an accurate search for tender points of the outer ear by means of a specific pressure algometer. Once the most sensitive point has been identified, an acupuncture needle is placed in contact with it for about 10 s, without skin penetration. The expected effect is a quick and evident reduction of acute pain. If no appreciable variation in pain intensity occurs within the following 60 s, a second or third attempt is made on other previously identified tender points, until the point at which the patient notices a clear remission of pain is found. In this positive case, the same testing needle can be immediately used for therapy, completely penetrating the skin, and then extracted after about 30 min. Alternatively, a temporary needle can be implanted and left *in situ* for a variable period of time (1–15 days). This innovative technique allows the identification, with maximum accuracy, of the most effective ear acupoints on migraine pain during acute attacks.

Key words Acupoint selection • Ear acupuncture • Migraine • Pain

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Introduction

There is increasing evidence that acupuncture can be helpful in the treatment of migraine [1]. Whereas a certain number of studies have been conducted on migraine patients using somatic acupuncture, data on the application of ear acupuncture (EAP) in these patients are only anecdotal and there is an urgent need for substantial data.

EAP was discovered towards the end of the 1950s when the French physician, Paul Nogier, observed patients with cauterizations on the outer ear carried out by healers to control sciatic pain [2]. His research spread rapidly all over the world, especially in China, where acupuncturists drew an Auricular Points Chart. The Chinese chart shares several points with the French one, even if they do not perfectly overlap [3]. The concepts of "somatotopic organisation" and "auricular representation" of the different anatomical structures in the human body were consequently transferred into practice as points which the acupuncturist must detect with accuracy and stimulate adequately to get an evident therapeutic answer.

Experimental research on animals has brought evidence of some effects of EAP, such as decreased withdrawal syndrome in morphine-dependent rats [4], activation of the hypothalamic satiety centre in obese rats [5] and inhibition of neurogenic inflammation [6]. Research on man demon-

strated a significant release of β-endorphin in EAP-treated patients [7] and a variation of pain threshold applying TENS and He-Ne laser to the outer ear [8, 9].

Recent research highlighted the analgesic, anxiolytic and myo-relaxant effect of EAP. Romoli, in a group of patients with contusive pain, demonstrated a significantly greater reduction of pain in the EAP-treated group compared to the placebo group [10]. Alimi et al. showed that the stimulation of the appropriate acupoints was more effective than placebo for reducing cancer pain [11]. The anxiolytic effect obtained with the application of temporary needles was significantly greater, stimulating a set of appropriate points *vs*. a set of sham points [12]. Romoli et al. demonstrated with electromyography in 3 randomised groups of bruxism patients that auricular stimulation was more effective than non-stimulation in reducing the levels of tension of some masticatory and deglutitory muscles. In the first 2 groups the authors compared acupuncture with needle-contact of the same auricular area related with the hypertonicity of the above-mentioned muscles. The two different modalities resulted in a similar myo-relaxant effect, pointing out the therapeutic effect of simple needle contact without penetration [13].

As previously reported, a veritable therapeutic response is not obtained by stimulating the outer ear without previous diagnosis and an accurate search of the exact point to treat. Oleson et al. [14] were the first to introduce the term of "auricular diagnosis" in mapping the different representations of musculoskeletal pain. They used three different methods: the detection of tender points, the measurement of their electrical conductibility and the presence of skin alterations on inspection of the outer ear [14]. The rationale of the first method is that auricular areas corresponding to a painful district show increased tenderness in comparison with other areas related to non-painful parts of the body. For this purpose special algometers are used, with a 2-mm metal tip probe and a spring-loaded stylus, able to give a maximal pressure varying between 125 and 600 g. The rationale of electrical detection is that acupoints related to a pain problem show a lowered skin resistance compared to the neighbouring ones. The rationale of the third diagnostic method is that a chronic disease can be suspected by the observation of skin alterations of different types in the auricular area representing the affected organ or anatomical district. The acupuncturist generally employs at least one method to gather sufficient information for reaching a diagnosis.

There is a fourth method, the "needle-contact test", which has been reported above as a therapeutic modality, but which the Authors wish to propose in the following case report as a combined diagnostic/therapeutic method for controlling acute pain. The procedure is the following: once the most sensitive point is identified with the algometer (Fig. 1a), an acupuncture needle is placed on it for about 10 s without skin penetration (Fig. 1b). The expected effect is the reduction of acute pain: if there is no appreciable variation within the following 60 s, a second or third attempt on other identified tender points must be made, until the point at which the patient notices a clear remission of pain is found. In this case the same needle can be used for therapy and withdrawn after about 30 min, or alternatively a temporary needle can be implanted for a variable duration (1–15 days). The aim of this innovative technique is to obtain maximum accuracy for identifying the most

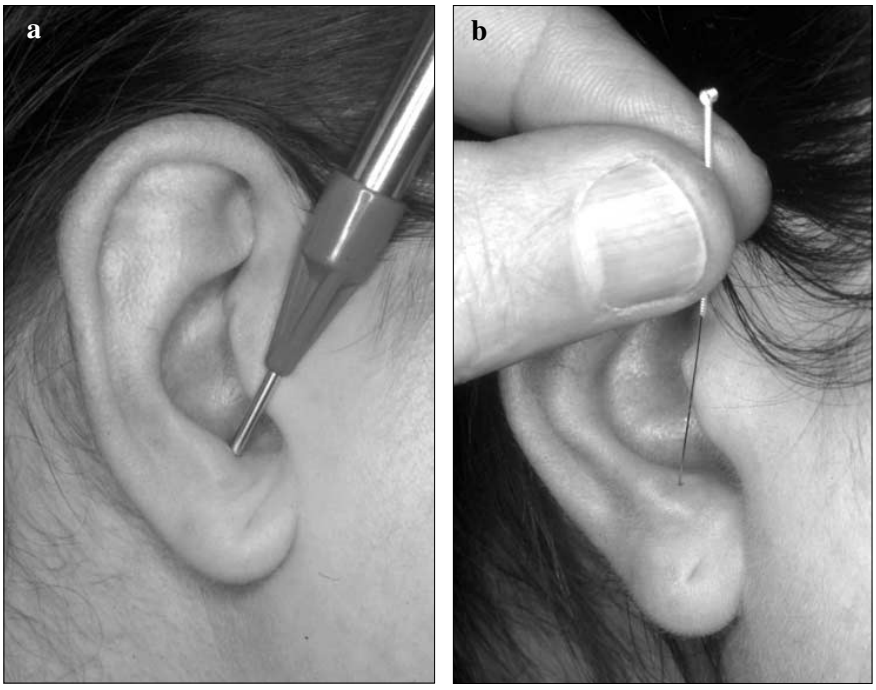

Fig. 1a,b Location of the most tender point detected by the pressure algometer (**a**) and needle-contact test (**b**)

effective points. The following case report describes needle-contact application in a patient during an acute attack of migraine without aura.

Case report

A 28-year-old female patient with acute migraine without aura consulted the Women's Headache Center at Turin University. The right-sided throbbing pain had started 3 h before and when she came in for consultation she had not yet taken any medication. She had been suffering for 15 years from migraine without aura, diagnosed fulfilling the International Headache Society's criteria [15]. The attacks, with a frequency of 8–10 times a month, were usually of moderate intensity and accompanied by nausea and phonophotophobia. Migraine occurred particularly, but not exclusively, during the perimenstrual period. Nimesulide was the analgesic drug she usually took, but it had lost its efficacy over the last few months in coincidence with an increase of migraine intensity, probably due to growing responsibilities at work. The response to triptans was good but the patient feared possible side effects, even though she never really experienced them.

We proposed controlling her pain with EAP and she gave her consent to treatment. Both outer ears were examined with a special pressure algometer able to produce a maximum pressure of 250 g at the tip. The right ear, homolateral to migraine, was clearly more sensitive and a very tender area on the superior and anterior portion of the antitragus was identified. The area, after disinfection with alcohol, was thoroughly explored with the algometer's tip until a very sensitive point was found on which a needle of Chinese manufacture (length 25 mm, diameter 0.25 mm) was lightly applied without skin penetration. At this first attempt a clear reduction in pain was obtained. Immediately after, the needle was pushed down about 2 mm into the cartilage and rotated once in a clockwise/anticlockwise manner. After this manipulation, the needle was not touched again for the whole period of insertion (30 min). The pain level, measured by means of a Visual Analogue Scale (VAS) on a 10 cm vertical line, was 56 before starting acupuncture. After 10 min the pain dropped to 25 (a reduction of 55.4% after the beginning) and after 30 min it had dropped to 20 (a reduction of 64.3%). Before the patient's dismissal the needle was removed and replaced with a temporary sterile single-use steel implant (Sedatelec, Irigny, France) (Fig. 2a), which the patient was invited to wear until at least the next day (Fig. 2b). These spear-headed implants are 3.4 mm long and have a cylindrical head with 1.2 mm diameter and height. The maximum diameter of the part of the needle that enters the skin is 0.7 mm. Each implant is at the end of a small sterile plastic container that contains compressed air. Locating the end of the container at the acupuncture point and putting pressure on the container releases the implant [11].

The patient had to measure pain intensity again at home 60 min, 120 min and 24 h after the treatment. The patient returned to consultation 2 days later and reported the following VAS values: 18 (60 min), 15 (120 min) and 21 (24 h). She was satisfied with the result and was still wearing the needle, which was well tolerated without any side effects.

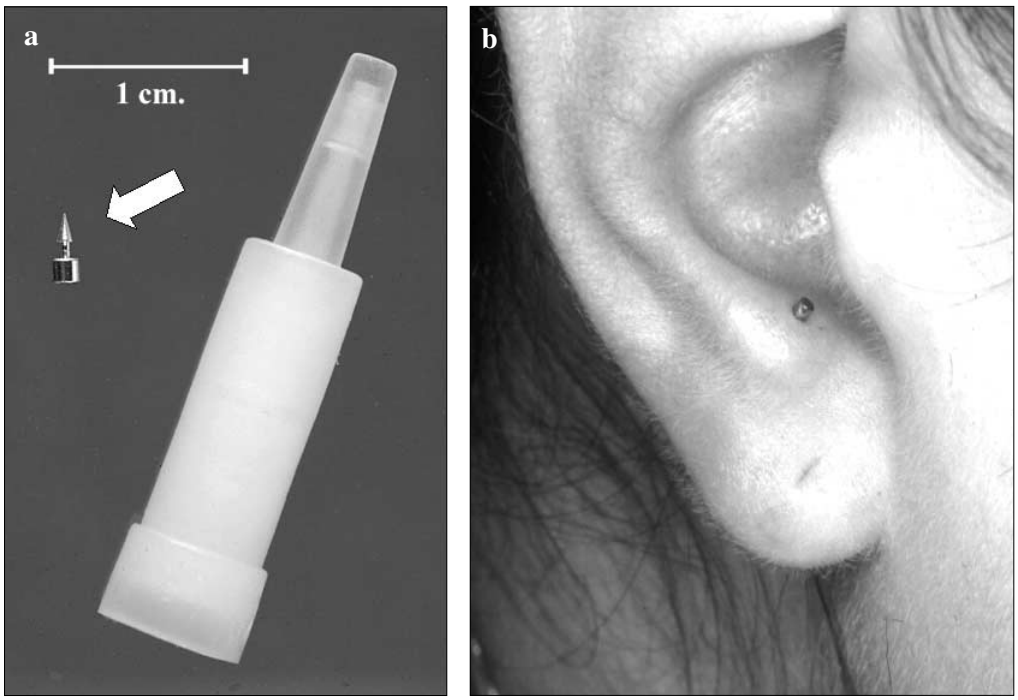

Fig. 2a,b Sterile steel implant with its container (**a**) and correct insertion of the needle implant (**b**)

Discussion

From this case report the possibility emerges to treat migraine pain with EAP using a method, the needle-contact test, which at the same time allows diagnosis and stimulation of the most effective point for a given patient. Unlike body acupuncture, which selects points for treatment whose locations have been handed down for centuries and are now consolidated, EAP treats points which have to be detected at every session and may vary from one session to the other in the same therapeutic course.

The efficacy of simple needle-contact highlights the potential of EAP in addressing migraine attacks. It is particularly noteworthy that the technique, when efficient, impacts pain in a very short time (within 60 s from the application of the needle on the point sensitive to pressure) and could therefore be considered a very active non-pharmacological aid in treating acute migraine pain particularly in patients who are inclined to analgesic drug abuse with the consequent risk of developing chronic headache. In any event, the case presented needs to be confirmed in a study with a higher number of patients and compared to placebo stimulation.

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ORAL COMMUNICATION

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Naratriptan in the short-term prophylaxis of pure menstrual migraine

Abstract Menstrual migraines are particularly difficult-to-treat. Few studies on the use of triptans in short-term prophylaxis of menstrually related migraine have been recently conducted, but evidences of triptans' efficacy in the specific case of pure menstrual migraine (PMM) are lacking.
The aim of this study is to explore the efficacy and tolerability of naratriptan as short-term prophylaxis of pure menstrual migraine (PMM) attacks. A multi-centre, open, non comparative, pilot six-month study was conducted in women, aged 18 years or older, with regular menstrual cycles and with a history of migraine without aura exclusively associated to the perimenstrual period. After an observation period of three months, patients took for three consecutive menstrual cycles oral naratriptan 1 mg twice daily, starting two days before the expected onset of menstruation and continuing for six days. Ninety-eight women with a history of PMM were screened for study participation, and 61 entered the study. Fifty-nine comprised the intent-to-treat population. The mean number of PMM attacks decreased from 3.5±1.4 in the 3-month observation period to 1.6±1.3 in the 3-month treatment with naratriptan. The pecentage of responders (subjects who recorded a decrease – equal or more than 50% – in the mean number of attacks) was 61.4%. A tendency towards a decrease in headache severity and in the presence of associated symptoms was observed during treatment. At least one adverse event during the treatment period was reported by 19 patients (31.1%). No serious adverse events occurred. Naratriptan may be an effective and safe treatment option in the short-prophylaxis of PMM.

Key words Short-term prophylaxis • Efficacy • Naratriptan • Pure menstrual migraine • Safety

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Introduction

Although at least 60% women with migrane complain of the presence of a painful attack related to the perimenstrual period (PMP), a lower percentage of them (about 10%) recognises the menstrual cycle as the only trigger of migrane attacks [1].

In general, menstrual attacks result longer and less responsive to the acute therapy than the extramenstrual ones [2]. In recent years a short-term prophylaxis, and namely a cyclic treatment to be taken only during the PMP, when attacks are supposed to occur, has been proposed as a treatment option for menstrual migraines. Different drugs have been used [3], with treatment periods ranging from 5 to 14 days, depending on the drug and on the clinical characteristics of the attacks.

Since 1998, when Newman et al. [4] proposed sumatriptan as mini-prophylaxis therapy for the menstrual attack, the attention of some researchers has been focused on the use of triptans for this specific aim. As a result, some papers reported the efficacy of those triptans with a longer half-life as

naratriptan [5] and frovatriptan [6]. The majority of authors, nevertheless, studied the most common type of menstrual migraine, the menstrually-related migraine (MRM), while clinical data addressed to the pure menstrual migrane (PMM) are quite rare.

The aim of this study was to evaluate the efficacy and tolerability of naratiptan, a triptan chemically related to sumatriptan, but which shows a greater bioavailability and a longer half-life (6 hours), in the short-term prophylaxis of PMM attacks.

Methods

All eligible patients were women, aged 18–51 years, with regular menstrual cycles, with at least one year history of migraine without aura (as defined by IHS criteria [7]) exclusively occurring during the PMP. In the three months of observation, they were required to have at least one attack of migraine without aura per month, exclusively occurring in the period -2/+3 days in respect to the first day of menstruation and at no other times of the cycle. Patients presenting the onset of menstruation ±2 days in respect to the expected date were included in the study. If the cycle started more than 2 days than the expected date, the patient withdrew from the study. During the 3-month treatment period, patients took oral naratriptan 1 mg twice daily, starting 2 days before the expected onset of menstruation and continuing for a total of 6 days.

Eligible patients were screened in a migraine-free state (screening visit), where they provided medical history as well as concurrent medication information. Patients received a complete physical examination, including assessment of vital signs and an electrocardiogram. Patients were given diary cards to record their migraines. The use of the diaries was reviewed with the patients, instructing them to complete the 3-month baseline observation; every month they returned for a control visit. Visit 4, 5 and 6 were performed 7 days before the expected start of the next menstrual cycle; patients underwent an urinary pregnancy test, and then they were given the study medication for one PMP.

Patients were not enrolled if they had confirmed or suspected heart diseases, cerebrovascular pathology including stroke, uncontrolled hyperthension and any concurrent medical or psychiatric condition that, in the investigator's opinion, might affect the interpretation of efficacy and safety data or which otherwise contraindicated participation in a clinical trial. Moreover, patients were excluded if they were pregnant, breast feeding or sexually active and not using adequate contraceptive measures.

Ten Headache Centers in Italy were involved in the study, after receiving institutional review board approval. All patients signed an informed written consent prior to study participation.

The primary endpoint of the present study was the mean number of PMM attacks that occurred over three naratriptan-treated menstrual cycles compared to the observation period. Secondary endpoints were the proportion of responders observed at the end of the study (a *responder* was a patient who recorded a decrease – equal or more than 50% – in the mean number of attacks associated to menses during the treatment period with respect to the observation period); the severity of migraine; the presence/absence of accompanying symptoms (nausea, vomiting, photofobia, phonofobia); the patient's evaluation on study drug; the percentage of patients with adverse events (AEs) during treatment period. An AE was defined as any untoward medical occurrence following the use of study drug. A serious AE was defined as any medical occurrence that was fatal, life threatening, disabling, required hospitalization, or caused congenital anomaly in the offspring of a patient.

Analysis populations

Intent-to-treat-population (ITT): All subjects who took at least one dose of the study drug and filled in correctly the information in the diary card were included in the intent-to-treat population. The minimum requirement for diary card data was considered having at least 2 diaries for the observation period and 2 diaries for the treatment period. This population was the primary population for efficacy analyses. All the identified protocol violators were not excluded from this population, whereas all subjects with incomplete or incorrect diary card were excluded.

Safety population (SAF): All subjects who took at least one dose of study drug were included in the Safety population. This population was considered for safety and tolerability analyses.

Data analysis

As far as the ITT population is concerned, and when applicable, the data set was completed by replacing the data of missing visits with those of the last valid visit according to the Last Observation Carried Forward (LOCF) method. The number of attacks for missed diaries was replaced with the minimum number of attacks recorded in the other diaries, for the observation period, and the maximum number of attacks recorded in the other diaries, for the treatment period.

All the secondary efficacy variables were evaluated on the ITT population using only the prevalence analysis technique (analysis of observed data, not LOCF).

Results

Efficacy

Ninety-eight women with a history of PMM were screened for study participation, and 61 entered the study. Fifty-nine patients took at least one study drug dose and filled in correctly the diary cards (ITT population). Two patients did not record any attack of menstrual migraine during the observation period and were therefore excluded from the analysis.

All participants presented at visit 1, 2 and 3, and data for the analysis during the observation period were complete. For the treatment period the percentages of subjects performing visit 4, 5 and 6 were 93.2% (n=59), 88.1% (n=53) and 84.7% (n=50) respectively for the ITT population.

The mean age of the subjects in the ITT population was 37.9 years (SD=7.2) with a mean body weight of 58.2 kg (SD=8.3) and a mean height of 162.2 cm (SD=6.6).

The mean number of migraine attacks decreased from 3.5±1.4 in the observation period to 1.6±1.3 in the 3-month treatment period with naratriptan (LOCF analysis; 57 patients). Very similar data were obtained considering the prevalence analysis (48 patients), the attacks falling from 3.4±1.3 to 1.6±1.1.

The pecentage of responders was of 61.4% (35/57) with the LOCF analysis and 60.4% (29/48) with the prevalence analysis.

The data on headache severity and accompanying symptomatology, as well as those regarding the presence/absence of a PMM attack in each menstrual cycle considered, are summarized in Table 1. The severity of migraine tended to be worse before treatment with naratriptan: the percentages of severe migraines were 35.3%, 38.5% and 36.0% during this period, and they were 25.0%, 37.0% and 20.8% during the treatment period. The number of episodes of nausea decreased from 63.6%, 59.6% and 65.9% during the observation period to 39.1%, 56.0% and 54.2% during the 3-month treatment period. An analogous trend towards improvement after naratriptan use was observed for photofobia and phonofobia, while this trend was not evident for vomiting.

Figure 1 shows patients' evaluation on study drug during the 3-month treatment period, the percentages of patients who rated the treatment as positive (quite good, good or excellent) were never less than 64%.

Table 1 Summary (presence/absence, intensity and accompanying symptomatology) of PMM trend during the study

	Obs 1st m n=59		Obs 2nd m n=59		Obs 3rd m n=59		Treat 1st m n=59		Treat 2nd m n=53		Treat 3rd m n=50	
Pts without PMM, % (n)	13.6 (8)		11.9 (7)		15.3 (9)		59.3 (35)		49.1 (26)		52.0 (26)	
Pts with PMM, % (n)	86.4 (51)		88.1 (52)		84.7 (50)		40.7 (24)		50.9 (27)		48.0 (24)	
Mild	25.5		11.5		6.0		25.0		11.1		33.3	
Moderate	37.3		42.3		44.0		50.0		51.9		45.8	
Severe	35.3		38.5		36.0		25.0		37.0		20.8	
Symptoms	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
Nausea, %	36.4	63.6	40.4	59.6	34.1	65.9	60.9	39.1	44.0	56.0	45.8	54.2
Vomiting, %	82.9	17.1	80.0	20.0	74.3	25.7	90.5	9.5	83.3	16.7	77.3	22.7
Photofobia, %	30.6	69.4	38.8	61.2	34.1	65.9	50.0	50.0	32.0	68.0	45.8	54.2
Phonofobia, %	37.5	62.5	35.4	64.6	34.1	65.9	59.1	40.9	41.7	58.3	50.0	50.0

Obs, observation period; *Treat*, treatment period; *m*, month; *N*, no; *Y*, yes

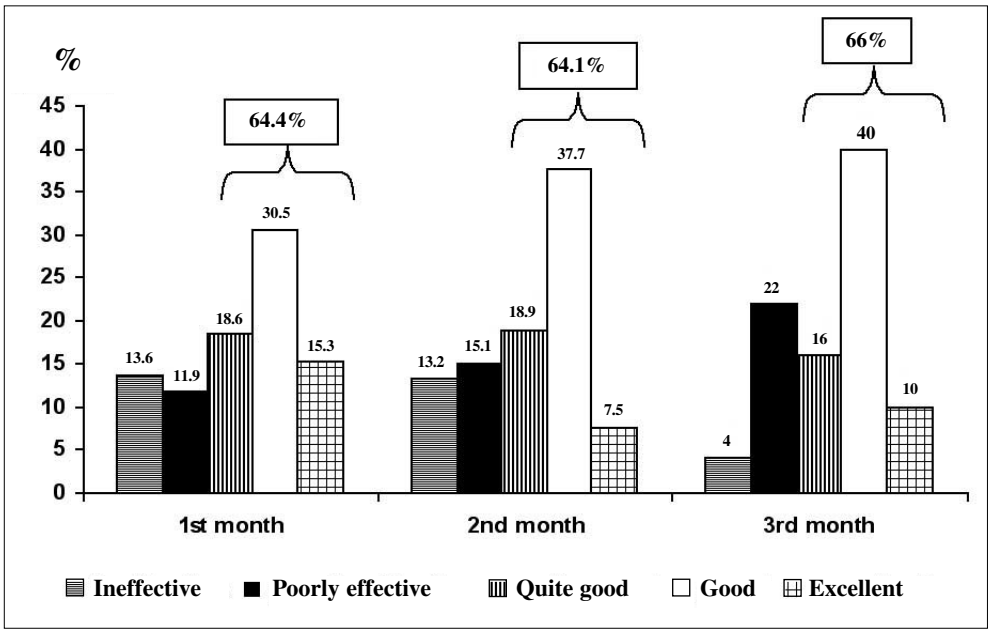

Fig. 1 Patients' rating of drug effectiveness

Table 2 Lists of adverse events reported by the patients (n=61) during naratriptan treatment

Event (n pts. with event)	Events, n (%)	Mild, n	Moderate, n	Severe, n
Pharyngitis/flu (5)	7 (11)	4	2	1
Dizziness (4)	5 (8)	2	2	0
UTI infection (3)	3 (5)	1	2	0
Headache (2)	2 (3)	0	2	0
Sleepiness (2)	2 (3)	2	0	0
Chest pressure (1)	1 (1)	1	0	0
Tachicardia (1)	1 (1)	0	1	0
Hypotension (1)	1 (1)	1	0	0
Myalgia (1)	1 (1)	1	0	0
Miscellaneous (5)	5 (8)	3	1	1

Safety

Based on the safety population sample (n=61), a total of 19 (31.1%) patients reported a total of 28 AEs (Table 2). The AEs were generally of mild to moderate intensity and spontaneously remitted. Two AEs, scored as severe, were pharingitis and depressed mood. No serious AEs occurred. The safety profile of naratriptan was consistent with that from other studies [8, 9].

Discussion

Naratriptan is a selective serotonin agonist chemically related to sumatriptan. Its interaction with 5-HT 1B/1D receptors is greater than sumatriptan. Moreover, naratriptan is more lipophilic, has a longer plasma half-life (6 hours) and an higher oral bioavailability than sumatriptan. The global incidence of AEs, particularly the neurological and chest sympthoms, does not differ from placebo at 2.5 mg dose.

These data suggest that naratriptan could represent a therapeutical option for short-term prophylaxis, and not only a valid acute drug to treat migraine attacks. In fact, naratriptan should be considered as a drug of choice for the short-term prophylaxes, in particular for menstrual migrane. The present study confirms this hypothesis. This was the first study designed to assess the efficacy of naratriptan as short-term prophylaxis in PMM showing the efficacy and tolerability of this triptan when it was administered at 1 mg bid during the perimenstrual period**.** Over 60% of the treated patients resulted as responders, and the average of the PMM attacks decreased from 3.5 during the observational period to 1.6 during the treatment period.

The mechanisms through which naratriptan exerts this positive prophylactic action remains still unclear: it may act peripherally to prevent the neurogenic inflammation that occurs during the PMP, with declining oestradiol levels [10] and rising prostaglandin (particularly of the E type) levels [11, 12].

In conclusion, a regularly menstruating woman with PMM could benefit from a short-term prophylaxis with naratriptan, which, in this pilot study showed potential efficacy and was generally safe. It must be noted that the cyclic perimenstual naratriptan treatment may offer an adequate answer to those women suffering from menstrual migraine attacks which in fact are particularly difficult-to-treat, as they tend to be longer and less responsive to acute treatments than the extramenstrual ones.

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EPIDURAL BLOOD PATCH IN HEADACHE BY SPONTANEOUS CSF LEAK

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Objective To evaluate the efficacy of epidural blood patch (EBP) in the treatment of headache by spontaneous CSF leakage (SCSFL).
Background Spontaneous intracranial hypotension (SIH) generally results from spinal spontaneous CSF leakage. EBP has emerged as the most important nonsurgical treatment for SCSFL. We have attempted to determinate the efficacy of EBP in the treatment of headache by SCSFL.
Design/methods We observed 24 patients with SCSFL seen from 1992 through 2004. In six patients (4 women and 2 men with age ranging from 31 to 66 years, mean 44 years) we performed EBP treatment. Follow-up, ranging from 6 months to 2 years, was obtained through neurological examination and telephone calls. All patients received EBP using 15 to 30 ml (mean 23 ml) of autologous blood.
Results All patients presented orthostatic headache. Other less common manifestations were nausea, vomiting, mild neck stiffness, tinnitus and hearing impairment, blurred vision, diplopia, and bilateral upper limb numbness. All symptoms worsened with orthostatic position. Spinal taps were performed in 4 patients. The level of the leak was determined with neuroradiological studies in 4 patients. All 6 patients failed an initial conservative treatment that ranged from 2 to 13 months (median 3.5) and consisted of bedrest, analgesic and hydration. With first EBP 5 patients (83%) became entirely asymptomatic within a few weeks; one patient, who had failed the first and second EBP, responded only to a third EBP. In 3 patients, EBP was given at the lumbar level where we found the leak, instead 1 patient with cervical CSF leak received EBP at a different levels of the leak, in lumbar side. "Blind" lumbar EBP was performed in 2 patients. All patients during and after injection remained in Trendelemburg position, approximately 30°, for 24 hours. Headache relief was obtained immediately.
Conclusions Our data confirm the efficacy of EBP in SCSFL. However, EBP is considered the treatment of choice in those patients who have failed the initial conservative treatments. Our data suggest also the efficacy of "blind" lumbar EBP and mainly the importance of prolonged Trendelemburg position, never reported in literature.

TRIGEMINAL SENSORY PATHWAYS FUNCTION IN SUNCT

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Short lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) is a rare primary headache characterized by pain referred to the orbital/periorbital area. Given the location of pain, the beneficial effect of surgical decompression of the trigeminal nerve and the clinical similarities with trigeminal neuralgia (which is caused by a trigeminal nerve dysfunction) an involvement of the trigeminal sensory pathways has been supposed in SUNCT. We studied trigeminal reflexes and laser evoked potentials (LEP) in 11 patients with SUNCT. Patients with idiopathic SUNCT (n=10) had no significant differences in latencies, amplitude and duration of all reflex responses between normal and affected side whereas 1 patient with symptomatic SUNCT due to a cholesteatoma of the cerebello-pontine angle had absent LEPs after stimulation of the affected supraorbital region. Our findings demonstrate that trigeminal sensory pathways are spared in idiopathic SUNCT and suggest that neurophysiological examination may differentiate the idiopathic and the symptomatic form.

LEVETIRACETAM IN THE PROPHYLAXIS OF NEW DAILY PERSISTENT HEADACHE

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Levetiracetam, s-eniantomer of piracetam, is a drug recently introduced for the care of epilepsy. The use of antiepileptic drug in the prophylaxis of headache is not an innovation and find its explanation in the fact that both the pathologies rise in an hyperactive brain with similar physiopathologic mechanisms and analogous clinical manifestations. The mechanism of action of levetiracetam is unknown, but this drug seems to be active only on abnormal neurons, by a selective inhibition on N type voltage-dependent Ca^{++} channels and by stabilizing neuronal hyperexcitability. This open-label study wants to test the efficacy of levetiracetam in the prophylaxis of *New Daily Persistent Headache* according with criteria of new IHS classification. Thirthy-four outpatients (7 men, 29 females; mean age 32.61 years; SD=8.96 years), all referred to the Headache Center of Santa Marta Hospital in Catania, have been enrolled. At the initial screening, all patients included in study received a diary card for data collection at baseline, after 1 month, 2 months and 3 months. The therapy started after second visit (1-month) at the initial dosage of 500 mg/day and increased by 500 mg every 5 days up to target dosage of 2000 mg/day. Two patients did not complete the treatment. At baseline, patients reported headache for a mean of 17.47 days per month (SD=1.76). After 3 months, 9 of the 32 (28.12%) patients who completed the study reported a complete positive treatment response and the others (71.88%) a decrease in the intensity and number of attacks. The frequency of attacks passed from a mean of 17.47 to a mean of 4.05 per month (SD=2.92). Twenty-six patients (81.25%) did not report any side-effect. The others reported asthenia, easy irritability, aggressiveness, but all always well tolerated. These results confirm the effectiveness of levetiracetam in the prophylactic treatment of *New daily persistent headache*, but they should be validated with double-blind controlled studies.

CEREBROSPINAL FLUID AND SERUM NEURON-SPECIFIC ENOLASE IN ACUTE BENIGN HEADACHE

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Neuron-specific enolase (NSE) is an enzyme contained in relatively large amounts in neurons, peripheral nervous system tissue and neuroendocrine cells; for this reason NSE is one of the most investigated biochemical markers of nervous tissue damage. We determined the cerebrospinal fluid (CSF) and serum NSE concentrations in 19 patients (16 women; mean age 47.7±16.3 years, range 23-78) referred to the Emergency Department because of acute headache. All patients resulted normal at neurological examination and presented normal findings at head CT scan and CSF examination; the mean time interval between headache onset and CT scan was 39.4±41.1 hours, whereas the interval between headache onset and CSF examination was 64.1±55.8 hours. Two patients also had MR study of the brain; cerebral angiography was

performed in one further patient. The final diagnoses were: migraine without aura (n=6), primary exertional headache (n=3), primary cough headache (n=1), tension-type headache (n=4), essential headache (n=4), mixed migraine and tension-type headache (n=1). CSF and serum NSE concentrations, and CSF/serum ratio of the patients were compared with the value of the same parameters of a control group (108 healthy subjects, 40 women, mean age 68.7 years, SD=16.7, range 19-92) by means of univariate ANOVA after correction of age as covariate. CSF NSE concentration was 14.16 ng/ml (95% C.I.=11.86-16.47) in the headache sample *vs*. 17.19 ng/ml (95% C.I.=16.23-8.15) in the control group; serum NSE concentration was 7.50 ng/ml (95% C.I.=5.20-9.80) in the headache sample *vs*. 8.45 ng/ml (95% C.I. 7.67-9.23) in the conrol group. CSF/serum ratio was 2.81 (95% C.I.=2.21-3.40) in the headache sample *vs.* 2.23 (95% C.I.=2.03-2.42) in the control group. Based on these findings acute benign headache is not associated with neuronal damage as determined by means of CSF and serum NSE concentration determination.

HABITUATION OF C02-LASER EVOKED RESPONSES AND PAIN SENSITIVITY DURING INTERICTAL PHASE OF MIGRAINE

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The habituation to various sensory stimuli is reduced in migraine patients. In previous studies, during migraine attacks patients showed a pattern of increased amplitude of laser evoked potentials (LEPs) and decreased subjective pain threshold. Moreover, during interictal phase, a reduced habituation of LEP amplitudes in response to repetitive noxious stimuli was found in respect with control subjects. The aim of the present study was to assess the habituation of both LEPs and pain sensation during interictal phase in migraine patients, in comparison with healthy controls. Twelve migraine patients (3 males and 9 females, aging between 20 and 50) were selected and compared with ten control subjects (5 males and 5 females, aging between 25 and 40). All subjects underwent a recording session with three scalp electrodes, placed at Fz, Cz and PZ and referred to the nasion. The pain stimulus was induced by laser pulses, generated by CO2 laser, delivered upon right and left supraorbital zones. The intensity of stimulation corresponded to subjective pain perception, measured by a visual analogue scale. Pain Rating Score (PRS) was calculated by means of subjective pain perception values. Patients were evaluated during attack-free conditions. Latency and amplitude of N2a-P2 complex were considered. The LEPs habituation was studied by measuring the changes of LEP amplitudes across and within three consecutive repetitions of 20 not-averaged trials each, with an interstimulus interval of 10 s. In migraine patients, the N2a-P2 waves amplitudes did not show a tendency toward habituation across and, above all, within the three repetitions, which correlated with the lack of habituation of PRS, in comparison with control subjects. Our results suggest an abnormal cortical excitability in migraine, causing the altered habituation pattern of LEPs under repetitive painful stimulation: an anomalous behaviour of nociceptive cortex during the interictal phase of migraine may predispose patients to headache occurrence and persistence.

HYPNIC HEADACHE: ACTIGRAPHIC AND POLYSOMNOGRAPHIC STUDY OF A CASE

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Introduction Hypnic headache (HH) is a primary headache characterized by a close relation to sleep. HH is a rare disorder; few studies have addressed its polysomnographic features.
Case report A 54-year-old woman had suffered from strictly nocturnal episodes of headache for the past three years. Typically, the attack occurred in the second part of the night and awakened her. The pain lasted up to 60 minutes after the awakening, and she sometimes took indomethacin without benefit. She presented episodes of headache almost every night, sometimes even twice per night. The pain dull, localized at the vertex and in frontal regions, bilaterally. Intensity ranged from moderate to severe. Nausea, photophobia and phonophobia were never present. The patient did not refer any sign of autonomic activation. No daytime headache was reported.
Methods The patient underwent a sleep study including actigraphy and 3 polysomnographic (PSG) recordings, before and after amytriptiline.
Results General physical and neurological examinations were normal, Body Mass Index was 27.4, and blood pressure was 130/80 mmHg. There was no pain or tenderness over the cervical region. TC, Angio-MRI and EEG were normal. Actigraphy revealed that motor activity during sleep was reduced during the nights with headache. PSG showed that the headache episodes observed occurred during REM sleep; the amount of REM sleep was below normal values, and increased after pharmachological treatment. Sporadic obstructive apneas and hypopneas were observed. Sleep microstructure analysis, performed according to the Cyclic Alternating Pattern model, showed an increased sleep instability after the treatment.
Conclusions Our data confirm the occurrence of HH during REM sleep, and support the hypothesis of hypoarousal as a pathogenetic mechanism for hypnic headache.

ATYPICAL ACUTE BARBITURATE WITHDRAWAL. CLINICAL REPORT

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We report the atypical clinical and EEG characteristics of an acute barbiturate-containing drug withdrawal of 5 patients suffering from lasting migraine with and without aura, abusers of butalbital-containing drugs (Optalidon), and without a previsiously history of psychiatric disorders. All patients assumed more than 750 mg of butalbital-containing drugs daily: usually these patients with acute withdrawal of butalbital presented anxiety, grand mal seizures and an EEG pattern characterized by the presence of waves and sharp-waves at the surface-EEG recording. Moreover our patients showed an acute confusional state with delusion and an EEG pattern characterized by slowly background activity, without sharp and sharp waves. None of them had grand mal seizures, or other parossisms. All symptoms disappeared after 2 or 3 days with administration of 100 mg/daily of Phenobarbital im and the EEG pattern was normal. Our date support the hypothesis that patients without psychiatric history, with delusion and an acute confusional state may complain an acute withdrawal of butalbital containing-drugs.

MIGRAINE, CELIAC DISEASE AND CEREBRAL CALCIFICATIONS: A NEW CASE

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We present a patient with migraine (with and without aura) in whom neuroimaging revealed cerebral calcifications in the occipital and parietal regions bilaterally. Visual examination showed bilateral double scotoma, and further investigations revealed celiac disease. She was a 31-year-old woman who started to suffer from attacks of pulsating unilateral parieto-temporal head pain, associated with nausea, photophobia and asthenia from the age of six years. The attacks were preceded by visual disturbances (point of light slowly growing to a crescent shape, followed by hemianopsia, usually on the left side) lasting five to 60 minutes. From age 22, she has complained of constant visual disturbances which take the form of a fixed white (blind)

spot in the centre of the visual field. She also reported pain attacks (frequency 2-3 per month) closely similar to her pre-existing migraine, but without visual disturbances. As a child she had suffered microcytic anemia not further investigated or characterized, an undiagnosed skin condition, and diarrhea. Cerebral CT showed calcifications at the cortical-subcortical junction in the occipital and parietal regions bilaterally. Eye examination showed visual acuity 10/10 bilaterally and normal fundus, while visual field examination showed bilateral double scotoma. Laboratory tests revealed microcytic anemia. Celiac disease was suspected, and the patient proved positive for antigliadin antibodies (IgG). Duodenal biopsy confirmed celiac disease. Celiac disease is sometimes associated with neurological complications. Only one case of celiac disease associated with migraine and cerebral calcifications has been reported. Even if the association between migraine and celiac disease could be coincidental since both are a common condition, our case seems important for two reasons. Firstly, although celiac disease plus migraine, and celiac disease plus bilateral occipital calcifications have been reported in some cases, only one case in which all three features are present together has been reported. Secondly, celiac disease was identified only after migraine had been diagnosed, suggesting that migraine may on occasion be a sentinel symptom for mild or undiagnosed celiac disease.

TRIGEMINAL AUTONOMIC CEPHALGIAS: A CONTINUUM CLINICAL SPECTRUM

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Two main groups of primary unilateral short-lasting headaches are known: those forms exhibiting marked craniofacial autonomic phenomena and those without autonomic activation. The former group, named trigeminal autonomic cephalgias (TACs) comprises cluster headache (CH), paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache (SUNCT). Trigeminal neuralgia is the main form without autonomic phenomena. These syndromes represent a unique clinical model for comprehension of head pain physiopathology. Despite unquestionable differences between the mentioned syndromes, some patients show coexistence of unilateral short-lasting headaches with and without autonomic craniofacial phenomena (e.g. cluster headache and trigeminal neuralgia in the same patient) or a shift of symptoms. This suggests a common pathophysiological background between unilateral short-lasting headaches with and without autonomic phenomena. We describe two patients suffering from separate strictly unilateral short-lasting headaches with and without autonomic features. These attacks were diagnosed as PH, SUNCT and trigeminal neuralgia according to the International Headache Society (IHS) criteria. Posterior hypotalamic activation has been demonstrated in SUNCT, CH and trigeminal neuralgia but not in other headache forms. We propose that the common pathophysiological background of TACs and trigeminal neuralgia is in the central nervous system at hypothalamic level. Our hypothesis is strongly supported by the observation that continuous electrical stimulation of posterior hypothalamus is effective in treating otherwise drug-resistant CH, SUNCT as well as trigeminal neuralgia.

A CASE OF SUNCT SECONDARY TO MULTIPLE SCLEROSIS

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Short-lasting Unilateral Neuralgiform Headache attacks with conjunctival injection and tearing (SUNCT) syndrome is a rare form of primary headache disorder, although secondary causes are well know. This syndrome is predominant in males, with a mean age of onset around 50 years. The attacks are strictly unilateral, generally with the pain confined to the ocular/periocular area. The attacks are moderate to severe in intensity and burning, stabbing or electrical in character. The mean duration of paroxysms is 1 minute, with a usual range of 10 to 120 seconds (total range 5 to 240 seconds). Ipsilateral conjunctival injection and lacimation accompany the attacks. Nasal stuffiness/rhinorrhoea are frequently noted. The attacks predominate during the daytime.
We report a new case of SUNCT syndrome secondary to multiple sclerosis in a 56 years old woman. The MRI of the head is positive for lesions in white matter with one lesion localized into the pons in the trigeminal nucleus, ipsilateral to the pain. The CFS was positive for oligoclonal bands. The patient for a long period had been treated without success with carbamazepin, gabapentin and phenytoin. A cycle of steroid treatment has determined a complete disappearance of the SUNCT attacks. We hypothesize that the lesion to the ipsilateral trigeminal nucleus caudalis might have contributed to the clinical picture of SUNCT.