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ORIGINAL

Recommendations for headache service organisation and delivery in Europe

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Abstract Headache disorders are a major public-health priority, and there is pressing need for effective solutions to them. Better health care for headache—and ready access to it—are central to these solutions; therefore, the organisation of headache-related services within the health systems of Europe becomes an important focus. These recommendations are the result of collaboration between the European Headache Federation and *Lifting The Burden*: the Global Campaign against Headache. The process of development included wide consultation. To meet the very high level of need for headache care both effectively and efficiently, the recommendations formulate a basic three-level model of health-care organisation rationally spread across primary and secondary health-care sectors, taking account of the different skills and expertise in these sectors. They recognise that health services are differently structured in countries throughout Europe, and not always adequately resourced. Therefore, they aim to be adaptable to suit these differences. They are set out in five sections: needs assessment, description of the model, adaptation, standards and educational implications.

Keywords European Headache Federation · Global Campaign against Headache · Guidelines · Headache disorders · Service delivery and organisation

Introduction

The mission statement of the European Headache Federation (EHF) sets out its primary purpose: to improve life for those affected by headache disorders in Europe [1]. EHF undertakes a range of activities in pursuit of this aim.

On behalf of the European Headache Federation and *Lifting The Burden*: The Global Campaign against Headache.

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"Educating Europe" about headache—its nature, prevalence, causes, consequences and management—is of highest importance. With knowledge of headache, and especially these aspects of it, comes recognition of headache disorders as a major public-health priority, and awareness of the need for effective solutions to them.

European Headache Federation is also much concerned with what these solutions should be, and how they might be implemented. Since better health care for headache and ready access to it are their essence, the organisation of headache-related services within the health systems of Europe becomes an important priority also to maximise both effectiveness and cost-effectiveness. These recommendations are the result of collaboration between EHF and *Lifting The Burden* (LTB), the Global Campaign against Headache [2, 3].

Headache disorders are amongst the top ten causes of disability in Europe [4]. Three of these (migraine, tension-type headache and medication-overuse headache) have major significance for public health and health-service policy because they are common and responsible for almost all headache-related burden. The principal objective of headache services within a health-care system must be to mitigate this burden; their focus must be these three disorders.

Other headaches, although generally much less common, are nonetheless important as they may be symptoms of underlying disorders that threaten health and well being. These secondary headaches call for correct diagnosis and effective treatment, which sometimes are required urgently to prevent serious consequences. Management of these is, essentially, treatment of the causative disorder, and therefore arguably belongs outside headache services. On the other hand, their recognition must be the responsibility of the services to which affected patients present; where headache is the symptom, this is likely to be headache services, which must make adequate provision for them also.

Purpose

Our aim was to formulate a basic model of health-care organisation rationally spread across primary and secondary health-care sectors and taking due account of the different skills and levels of expertise in these sectors.

We recognised, and endeavoured also to take into account, that health services are differently structured in countries throughout Europe, and not always adequately resourced.

The purpose of these recommendations is therefore to describe, and explain, a model for headache service organisation that

(a) meets the very high level of need for headache-related health care both effectively and efficiently;

(b) is adaptable to suit differing local heath service structures within Europe.

These recommendations are in five sections: needs assessment, description of the model, adaptation, standards, and educational implications.

Development process

The concepts on which these recommendations are based were first explored in a consultation document prepared by the British Association for the Study of Headache [5]. The working group behind that document included secondary-care headache specialists, primary-care physicians with an interest in headache and patient representatives and advocates. The context was, specifically, the National Health Service (NHS) in the United Kingdom; at the time, the NHS was undergoing reorganisation that favoured a general shift of health services from secondary to primary care.

The development group for these recommendations were six headache specialists from Denmark, France, Italy, Spain and United Kingdom. Pre-consultation proposals were published as expert opinions in 2008 [6]. The consultation group included members of the National Headache Societies within the European Headache Federation representing Albania, Belgium, Bulgaria, Denmark, France, Georgia, Germany, Greece, Italy, Norway, Portugal, Romania, Russia, Slovenia, Spain, Switzerland, Turkey and United Kingdom. The consultation process led to revisions and refinements by the development group and, thereby, the production of these recommendations.

Editorial independence

EHF was the sole funding body supporting development of these recommendations.

Headache-related health-care needs assessment

This assessment is based on data that exist and on a number of assumptions, which are explained below.

Amongst every 1,000,000 people living in Europe, there are

- 120,000 adults and 15,000 children in need[1] of professional health care for headache

[1] "Need" is defined here as existing only in those who are expected to seek access to professional headache care, when available, *and* are likely to benefit.

- requiring the equivalent of 33 doctors working full time in headache medicine.

Population-based studies indicate that amongst every 1,000,000 people living in Europe, there are

- 110,000 adults with migraine [4, 7], 90,000 of whom are significantly disabled [8];
- 600,000 people who have occasional other headaches, the majority being episodic tension-type headache and not significantly disabling;
- 30,000 adults with daily or near-daily headache [4], of whom most are disabled and many have medication-overuse headache.

Existence of a health disorder does not translate directly into need for professional health care. "Need" is generally defined with regard to potential for benefit (there is no need for something that will not be helpful in some way). The proposal that all of the people listed above would gain some benefit from headache care is clearly arguable, but the suggestion that they all have a *need* for care must be constrained in a resource-limited world.

Need predicated on anticipated benefit must rise above a threshold of benefit. Of course this is at the heart of health economics and policy. Thresholds are hard to set objectively, whilst needs assessments are highly sensitive to them. With regard to headache, many people treat themselves, some through necessity, but others from choice. Those who do so are not only those who are less severely affected [8]; many choose self-management when they expect the marginal benefit of professional involvement in their care to be small: sub-threshold benefit negates need. This itself is problematic, because patients' expectations are quite often unrealistic—either too low or too high—which means that needs assessment based on what people actually do has questionable validity. This is more the case when service improvement is planned: a better service—if "better" means delivering enhanced benefit—should see greater usage than a poor service ("discovered need"). This ought to be factored in, but it cannot readily be estimated.

Aside from these patient-driven highly relevant issues, another is also threshold dependent. Cash-limited health services seek value for money, and will discount needs, however great, whenever utility gain per unit of health-care resource consumption will be low. In headache medicine, this is probably not inequitable: the potential for benefit from professional health care is, generally, greatest amongst those worst affected. Health policy might reasonably focus on these, but perhaps not too restrictively: both migraine and medication-overuse headache are disabling but, in most cases, can be effectively treated at rather low cost whilst mismanagement commonly results in worsening. Health policy should acknowledge this also.

The approach to our needs assessment is conservative: in the face of uncertainty and a number of inestimables described above, it will under-rather than over-estimate need. In the following sections, we set out and explain our assumptions.

Numbers

A reasonable assumption, we suggest, for the purpose of assessing what should be provided is that only those with disabling headache are in need of professional care. This means, on the basis of the numbers above, 90,000 adults with migraine and 30,000 with daily or near-daily headache: 120,000 adults overall or about 15% of the adult population. There are empirical data from a large UK general practice that support this: 17% of registered patients aged 16–65 years consulted for headache at least once in 5 years [9]. In a Danish population-based study, 11% of adults had consulted a doctor within the last year because of headache [10].

For the child population, need is more difficult to quantify because there are fewer data. Headache is apparently as common in children as in adults, with a 1-year prevalence of >50% [4], but there are different characteristics. It is clear that migraine prevalence is lower in children, dependent upon age, and overall in Europe about half that in adults [4]. On this basis, a reasonable assumption is that, numerically, need for care arises at half the rate per head of that in adults: that is, in 7.5%, or in 15,000 children per 1,000,000 of the general population, where children make up 20% of that population.

Demand versus need

The issues have been discussed above. On the relationship between "need" (numbers who would benefit from health care) and "demand" (the proportion of those in need who seek health care), complex factors, not all well understood, govern health-care utilisation by people with headache [8]. One is the general lack of availability of care, or its poor quality, which is self-perpetuating until health-care provision is improved. This must be kept in mind, because any assumption about demand is sensitive to this. For the purposes of this assessment, many of the issues discussed earlier are discounted in pursuit of conservatism, and this should be recognised. It is assumed that demand for headache-related health care is expressed by only 50% of those who might be judged to be in need. This has some evidential support [8, 11].

Time

The need for inpatient management of primary headache is very low. Admission of headache patients with comorbidities,

and of patients with medication-overuse headache for detoxication, is sometimes good practice but, overall, fewer than 1% of presenting patients need inpatient care. They can be ignored in these calculations.

The multiple assumptions relating to time allocations, therefore, consider only ambulatory care. They are based on expert views of requirement, again tempered with conservatism.

1. The average consultation need per adult patient is 1.25 h per 2 years. This average is within a wide range of variation, mostly according to diagnosis but also subject to level within the health-care system: consultations in specialist care are usually longer (which may reflect case complexity). In the majority of cases, the total time will be made up of a longer first consultation, including diagnostic enquiry and impact assessment (up to 45 min in specialist care), and 1–3 shorter follow-up appointments in the first and subsequent years.
2. The average consultation need per child patient is greater: 2 h per 2 years. Expert opinion supports this, citing the need for enquiry into family dynamics, schooling and peer relationships as issues relevant to management success.
3. No wastage occurs through failures by patients to attend appointments. This assumption may appear manifestly false, but wastage of this sort is very difficult to predict in the context of proposals for service improvement. At present, such wastage is commonly discounted by overbooking.
4. Each full-time physician (or equivalent) provides 1,344 h of consultation time per year. One day per week is the minimum required for non-clinical work (administration, audit and continuing professional development); each week, therefore, allows 4 days, each of 7 h, of patient-contact time. Only 48 weeks are worked per year.

Service provision requirement

Despite the conservatism pervading these assumptions, the result is a very challenging estimate of service requirement, expressed in medical full-time equivalents (Table 1). Two conclusions follow.

First, beyond argument, is that most headache services *must* be provided in primary care. This is not a bad thing. Wherever health-care reform is in progress, there is emphasis on strengthening primary care [12]. In addition, and of specific relevance, most headache diagnosis and management requires no more than a basic knowledge of a relatively few very common disorders, which ought to be wholly familiar to primary-care physicians. Only standard clinical skills, which every physician should have, need to be applied. No special investigations or equipment are usually necessary. In other words, there is no good clinical objection to locating most headache services in primary care.

Second, headache services must be formally organised within the structure of local health services generally. If, instead, they merely develop ad hoc, as is currently the case in most of Europe, they cannot possibly be delivered efficiently or equitably.

A model of headache-service organisation

The fundamental purpose of the model is to divide service provision rationally between primary and secondary (specialist) care. Within a structured health-care system, management of patients at the lowest level commensurate with good care makes most efficient use of allocated resources and is the means by which effective care can reach more who need it. How this is best done clearly depends on the local general health-service structure and on the resources allocated.

However, it also depends on the percentage of presenting patients whose health-care needs cannot be met at primary-care level because of diagnostic or management complexity. Our expert estimate is that 10% of presenting patients might appropriately be treated at a higher level. There are empirical data to support this from a UK general practice: of the adult patients consulting for headache, 9% over a period of time were referred to secondary care [9].

We believe that not all of these require the highest levels of expertise, which is most likely to be available in academic specialist centres. In most countries these are few in number, and they would be overwhelmed if required to manage 10% of patients. We do not believe this is necessary: 1–2% is more realistic.

Accordingly, we recommend the following organisational model (Table 2), and believe it to be suitable for most European countries. As well as proposing services

Table 1 Estimated service requirements to meet headache-related health-care demand in a population

Estimated numbers of adults/children with headache care needs per 1,000,000 population	Expected demand (hours of medical consultation per year)
120,000/15,000	45,000 h (33 full-time equivalents)

Table 2 Headache services organised on three levels

Level 1. General primary care	• Frontline headache services (accessible first contact for most people with headache)
	• Ambulatory care delivered by primary health-care providers
	• Referring when necessary, and acting as gatekeeper, to:
Level 2. Special-interest headache care	• Ambulatory care delivered by physicians with a special interest in headache
	• Referring when necessary to:
Level 3. Headache specialist centres	• Advanced multidisciplinary care delivered by headache specialists in hospital-based centres

delivered on three interdependent levels, the model sets what are intended as minimum standards; these may be adapted in accordance with local national health service structure, organisation and delivery.

Level 1: General primary care

Non-specialist health-care providers in primary care should meet all of the needs of about 90% (see argument above) of people consulting for headache. At this level, most cases of migraine or tension-type headache should be competently diagnosed and managed. Other common primary and secondary headache disorders listed as core diagnoses (Table 3) should be recognised, but not necessarily managed. Referral channels to levels 2 and 3 should be in place for these cases and for patients who are diagnostically complex or difficult to manage.

On the assumptions above, one full-time practitioner can provide headache care at level 1 for a population no larger than 35,000.

Table 3 ICDH-II core diagnoses to be recognised at level 1 [13]

Primary headache disorders
1.1 Migraine without aura
1.2 Migraine with aura
1.2.3 Typical aura without headache
2.1 Infrequent episodic tension-type headache
2.2 Frequent episodic tension-type headache
2.3 Chronic tension-type headache
3.1.1 Episodic cluster headache
3.1.2 Chronic cluster headache
Secondary headache disorders
5.2.1 Chronic post-traumatic headache attributed to moderate or severe head injury
6.2.2 Headache attributed to subarachnoid haemorrhage
6.4.1 Headache attributed to giant cell arteritis
7.4.1 Headache attributed to increased intracranial pressure or hydrocephalus caused by neoplasm
8.2 Medication-overuse headache (and subtypes)
9.1 Headache attributed to intracranial infection
10.3 Headache attributed to arterial hypertension
11.3.1 Headache attributed to acute glaucoma
13.1.1 Classical trigeminal neuralgia

Level 2: Special interest headache care

Physicians at this level must offer "special interest" services, providing more advanced care to about 10% of patients who are seen at level 1 and referred upwards. Their competence should embrace diagnosis and management of more difficult cases of primary headache and some secondary headache disorders (Table 3), but not those that are very rare. To fulfil their role, they will need access to other services such as neurology, psychology and physiotherapy; for perhaps 10% of their patients they will require a referral channel to level 3.

One full-time physician can provide headache care at level 2 for a population no larger than 200,000.

Level 3: Headache specialist centres

These centres are likely to be academic. Expert physicians at level 3 should provide advanced care to about 1% of patients first seen at level 1 and referred upwards—either via level 2 or directly, and urgently when necessary. Level 3 should be supported by specialist neurological expertise, have full-time inpatient facilities (with a recommended minimum of two beds per million population) and access to equipment and specialists in other disciplines for diagnosis and management of the underlying causes of all secondary headache disorders, and it should concentrate experience in treating rare headache disorders such as the less-common trigeminal-autonomic cephalalgias.

Level 3 should support levels 1 and 2 through medical advice and education.

One full-time physician can provide headache care at level 3 for a population no larger than 2,000,000.

The gatekeeper role within the model

The model's essential purpose is to shift demand from secondary-care services and move it to primary care—a move which in general is cost saving [14]. The *gate-keeper*

role of primary care [15, 16] is a key issue: the model will not be workable if this role is not embedded at level 1, and patients are allowed to go directly to higher levels regardless of need.

More needs to be said on this. Unrestricted access to specialists induces a demand for costly and sometimes unnecessary services. Patients cannot be blamed for seeking access directly to those they perceive to be experts. Gate-keeping ostensibly guides patients efficiently and in their best interests through the system according to their needs, not their demands. Whatever may be the supposed purpose, gate-keeping probably contributes substantially to cost containment. More importantly, it is the means of preventing specialist services becoming over-loaded, a situation that denies specialist access to some who really need it.

The effectiveness of a system that employs gate-keeping [17], and the equity of it, both rely on efficiency at the level interfaces, seams in service continuity where breakdowns can occur readily and detrimentally to patients [18]. There should not be system-created delays or other barriers set against those who do need specialist care. This is why the model calls for interdependence, and facilitated referral channels, between the levels.

Adaptation

How this model might be implemented in practice depends not only on the quantity of resources allocated to headache services but also upon the general structure of the health service within which these services are accommodated. Adaptation of the model may be appropriate, and is possible in a number of ways.

Primary versus secondary care

Level 1 must be in primary care; numbers demand it, and other arguments to support this are expressed earlier. Level 3 centres equally clearly must be in secondary care (or tertiary care in countries that make this distinction). Level 2, on the other hand, can be in either primary or secondary care. Options range from neurologists or trained but non-specialist physicians in district hospital outpatient departments or in polyclinics to general practitioners with a special interest working in primary care (a popular development in the UK [19]).

Combined levels

There is no intrinsic reason why one centre cannot provide both levels 2 and 3 care. This should not replace any part of level 2 with level 3: this would result in loss of efficiency.

Level 1, by its nature, is or should be community based. It is possible nonetheless, and may be appropriate, for certain level 2 centres to offer, in addition, local level 1 care.

Division of caseload

The 90:9:1% split between levels 1, 2 and 3 are estimates of need in Europe as a whole, based on expert opinion.

Throughout Europe, there are variations in prevalences and characteristics of the common headache disorders [4], particularly the frequency of daily or near-daily headache [20, 21]. The division of caseload between levels may need some adjustment in particular countries. The model will accommodate this without fundamental change, but capacity at each level will need adjustment. Ideally this would be based on locally gathered empirical data.

Doctors versus other health-care providers

The model envisages doctor-provided services as the norm at level 1 and as essential at levels 2 and 3. Some countries in Europe are expanding the roles of other professionals in health care as policy. Where this is so, it may allow service delivery at level 1 by nurses or, where they exist, clinical officers trained medically but to a lower level than doctors.

The desirability of this is uncertain, but it is probably a good way forward if the alternative is nothing. Nurses by training are not diagnosticians, but that can be addressed by training. Nurses appear to be very good at follow-up in countries where they are permitted to undertake this role.

Standards

The following are recommendations as minima.

At level 1, physicians, physician-supervised nurses or clinical officers should:

- have completed a postgraduate theoretical training course in headache medicine;
- have the skills and competencies to diagnose and manage most patients with migraine with or without aura or episodic tension-type headache, following national or EHF guidelines [22];
- recognise other primary and secondary headache disorders listed as core diagnoses (Table 3);
- maintain their skills by practising headache medicine for half a day or more per week on average.

At level 2, physicians should

- acquire their expertise by completing a theoretical and practical training course in headache medicine;

- have the skills and competencies to diagnose and manage more difficult cases of primary headache (all migraine; frequent episodic and chronic tension-type headache; cluster headache and other trigeminal-autonomic cephalalgias) and some secondary headache disorders (chronic post-traumatic headache attributed to moderate or severe head injury; headache attributed to giant cell arteritis; all subtypes of medication-overuse headache; classical trigeminal neuralgia);
- use ICHD-II [13] in their practice;
- follow national or EHF management guidelines [22];
- maintain their skills by practising headache medicine on two days or more per week and by continuing training through regular contact with a level-3 headache centre.

At level 3, specialist physicians should:

- acquire their expertise by:
  - completing a residency programme attached to a level-3 headache centre over one year full-time (or equivalent); and
  - diagnosing and managing 1,000 unselected patients presenting to level 3, with a documented practice record; and
  - making at least two research presentations to national or international conferences and at least two educational lectures;
- apply a multidisciplinary approach in their practice, making use of equipment and specialists in other disciplines in order to diagnose and manage the underlying causes of all secondary headache disorders;
- maintain their skills by:
  - practising headache medicine on two days or more per week; and
  - carrying out or supporting research, and publishing;
- provide formal teaching in headache medicine.

Educational implications

It is crucial that better knowledge of headache and the use of evidence-based guidelines [22] in primary care keep the great majority of patients at level 1, reducing unnecessary demand upon specialist care. A similar requirement exists at level 2. There are major implications for training.

These need careful consideration. The start, although it is not easily achieved, is to give more emphasis to headache diagnosis and management in the medical schools undergraduate curriculum. This will ensure at least that newly qualified doctors will have some understanding of a set of burdensome and very common disorders—which is often not the case now. However, much more is needed beyond that, and more quickly. The EHF headache schools offer a theoretical and practical course meeting the initial training requirements of level 2 [23]. The Master's Degree course in headache medicine at Sapienza University, Rome [24, 25], offers a more advanced training-the-trainers course, but has even less reach. Training at national level has to be part and parcel of effective headache-service reform. The educational challenge is greatest at level 1, because of the weight of numbers of health-care providers who need training. Within the 3-level care system proposed, a training role for each higher level to the level below can be envisaged. It is likely that the entire structure will depend on these roles being developed.

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Conflict of interest None.

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REVIEW ARTICLE

Overview of diagnosis and management of paediatric headache. Part I: diagnosis

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Abstract Headache is the most common somatic complaint in children and adolescents. The evaluation should include detailed history of children and adolescents completed by detailed general and neurological examinations. Moreover, the possible role of psychological factors, life events and excessively stressful lifestyle in influencing recurrent headache need to be checked. The choice of laboratory tests rests on the differential diagnosis suggested by the history, the character and temporal pattern of the headache, and the physical and neurological examinations. Subjects who have any signs or symptoms of focal/progressive neurological disturbances should be investigated by neuroimaging techniques. The electroencephalogram and other neurophysiological examinations are of limited value in the routine evaluation of headaches. In a primary headache disorder, headache itself is the illness and headache is not attributed to any other disorder (e.g. migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalgias). In secondary headache disorders, headache is the symptom of identifiable structural, metabolic or other abnormality. Red flags include the first or worst headache ever in the life, recent headache onset, increasing severity or frequency, occipital location, awakening from sleep because of headache, headache occurring exclusively in the morning associated with severe vomiting and headache associated with straining. Thus, the differential diagnosis between primary and secondary headaches rests mainly on clinical criteria. A thorough evaluation of headache in children and adolescents is necessary to make the correct diagnosis and initiate treatment, bearing in mind that children with headache are more likely to experience psychosocial adversity and to grow up with an excess of both headache and other physical and psychiatric symptoms and this creates an important healthcare problem for their future life.

Keywords Headache · Childhood · Paediatric headaches · Diagnosis · Epidemiology · Defining features

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Definition

Headache is the most common somatic complaint in children and adolescents both in clinical and epidemiological databases. The incidence of childhood migraine and frequent headache has substantially increased over the last 30 years. The increased incidence is alarming and probably

reflects untoward changes in children's lifestyles. Primary headaches (especially migraine and tension-type headache, TTH) is the most important cause of headaches in this age group, but secondary headaches and unusual causes of headaches also have to be considered [1, 2].

Epidemiology of headaches

There is a high incidence, prevalence, and individual and societal cost of headache disorders in children and adolescents [3]. The reported prevalence of headache among schoolchildren varies greatly, from 5.9 to 82%, depending on the definition criteria [1, 4–6]. The vast majority of headaches is primary and classified as migraine or TTH.

Prevalence of headache increases throughout childhood reaching a peak at about 11–13 years of age in both sexes [7]. By age 3, headache occurs in 3–8% of children [8, 9]. At age 5, 19.5% have headache and by age 7, 37–51.5% have headache [10–13]. In 7–15-year-olds, headache prevalence ranges from 26 to 82% [12–14].

The studies based on parental reports may be an unreliable source of information on the frequency of headache in young children. It has been suggested that child-completed diaries and teacher observation forms should be used more widely [15]. A population-based study showed that almost 36% of the parents of children with headache are unaware of the headache [16]. Whether ID Migraine TM® is a useful tool in screening adolescent migraine is still under discussion [17].

Natural history of headache

According to several authors, longitudinal studies and repeated cross-sectional surveys are reported as essential for enhancing the knowledge about the prognostic development of pain disorders and perceived health in the younger population, and for further investigation of possible causal relationships and related factors. Recently, several clinical and epidemiological studies have been published on the long-term course of primary headaches in children and adolescents [18–27].

Natural history of migraine

Outcome research for paediatric migraine headaches is limited, thus restricting knowledge of the effectiveness of long-term management and outcome. Multidisciplinary treatment was found to be effective for children and adolescents with improvement of multiple outcome variants of paediatric migraine care, including frequency, severity, and school days missed [18].

Some important points could be summarised as follows;

- Diagnoses of primary headache subtypes change over time due to overlapping symptoms and possibly related to maturation.
- Long-term prognosis of headache is adversely affected by an initial diagnosis of migraine and by changing headache location, and it tends to be affected by an increasing time between headache onset and first presentation.
- Girls and children with frequent headache have a poorer prognosis and therefore intervention is particularly important in these groups.
- Stressful life events in childhood have an impact on the course of migraine and TTH and increase the possibility of combined headaches.
- Headache onset early in life increases the risk of an unfavourable clinical course and also genetic factors play an important role in the phenotypic expression of the disease.
- More long-term comprehensive population-based studies are needed in this area.

How to diagnose headache

A thorough evaluation of headache in children and adolescents is necessary to make the correct diagnosis and initiate treatment. The evaluation should include detailed history of children and adolescents (including parent and teacher observations, observations of child-carer, family relationships, medical history of children and parents) and completed by detailed general and neurological examinations. One has to keep in mind that some symptoms may be referred from the child's behaviour only (e.g. stopping to watch a favourite movie, interrupting a computer game, or the child's wish to go to bed in a quiet, darkened room during daytime). Children may also be asked to draw a picture of what their headache, since children, especially younger ones, communicate better through pictures than verbally [28, 29].

History

The history determines the correct diagnosis, so questions need to be directed to both the child and parents. The following questions should be included:

- Do you have one or more types of headache?
- How did the headaches begin?
- When did the headaches begin?
- Are the headaches progressive, staying the same or improving?

- How often does each headache type occur every month (or every day)?
- How long do the headaches last?
- Do the headaches occur at any special time or under any special circumstances?
- Are the headaches related to specific foods, situations, medications or activities?
- Are there warning symptoms before headache onset?
- Where is the pain located?
- What is the quality of the pain?
- Are there associated symptoms during the headaches?
- What do you do during your headaches?
- What makes the headaches better?
- Does anything make the headaches worse?
- Do symptoms continue between headaches?
- Are you being treated for or do you have any other medical problems?
- Do you take medication for any other problem on a regular on intermittent basis?
- Does anyone else in the family have headaches?
- What do you think is causing your headaches?
- How is your daily routine?

Useful strategies to help improve headache diagnosis in children might be the following:

1. Take the history with sufficient time and patience, and with age-appropriate terminology
2. Ask the patient (assisted by the parents) to keep an appropriate headache diary (e.g. depicting the main headache characteristics and associated symptoms) over a period of some weeks to document the headache frequency and duration, the degree of disability and the occurrence of associated symptoms as well as the use of medications.
3. Give yourself enough time for each patient visit. History should also include pregnancy period of mother, birth history, developmental history, injuries, operations and dietary habits of early childhood, school experiences, history of substance abuse, family relationships, socioeconomic and psychosocial status both of the child and parents.

Assessment of headache severity

Headache severity of children and adolescents should be quantified using a pain rating scale, visual analogue scale or other equivalents according to age and cognitive levels of subjects. Combined scales may be more useful than one way scales. Biological parameters of pain and observations of other family members should be noted also [30].

Physical examination

The examiners should keep in mind the tentative diagnosis and substantiate their clinical impression while performing general examination. Important clues should be noted, for example fever may indicate an infection, elevated blood pressure may indicate a hormonal or renal disturbance, growing abnormalities may indicate pituitary or hypothalamic disorders, petechia or palpable lymphadenopathies may indicate haematopoietic abnormalities, organomegaly may indicate a systemic neoplasm, atopic disorders may be related to migraine, and unexplained injuries of different ages may indicate child maltreatment [25, 31, 32].

Neurological examination

A complete neurological examination should be performed focussing particularly on level of consciousness, meningeal signs, visual disturbances, focal neurological deficits, disorders of coordination, gait and speech, auditory disorders, measurement of head circumstances, localised tenderness of scalp or any body areas. In addition, a psychiatric interview of children and parents should be performed when needed. In the majority of patients with primary headache disorders, the general physical and neurological examinations are normal [4, 33].

Psychological examination

Repeated pain experiences have some negative effects on daily living activities (i.e. sleep, appetite, play, attention, etc.). During the prepuberty and puberty period changes of emotional status and personality stand in the forefront. It should be differentiating whether the emotional problem or change is a comorbidity or the main problem. Symptoms of depression, which include sadness, tearfulness, withdrawal from activities, hopelessness, need to be checked.

It has been shown that migraine is not related to family and housing conditions, school situation, or peer relations, whereas TTH is associated with a higher rate of divorced parents and fewer peer relations [34]. As an associative comorbidity, the frequency of migraine headache in a clinic sample of Tourette syndrome subjects was nearly fourfold more than the frequency of migraines reported in the general population [35]. The evaluation process should be completed with scales (including depression, anxiety, self-esteem, CBCL, etc.) and family interview.

Laboratory tests

The choice of laboratory tests rests on the differential diagnosis suggested by the history, the character and temporal

pattern of the headache, and the physical and neurological examinations. On the contrary to migraine, detailed laboratory and imaging screen should be performed in case of migraine equivalents [36]. Subjects who have any signs or symptoms of focal/progressive neurological disturbances should be investigated by cranial computed tomography (CT) or magnetic resonance imaging (MRI) [37]. Emergency setting studies showed that neuroimaging (head CT scan or MRI) was performed on 8–41% of children, which on first glance appeared high given that 96% of all patients were ultimately diagnosed with a benign disease. However, 5.5–25% of those who underwent neuroimaging were ultimately diagnosed with a "pathological" process [38–41]. The electroencephalogram (EEG) and neurophysiological examinations (including VEP, event related potentials, EMG, etc.) are of limited value in the routine evaluation of headaches, except from "migraine-triggered seizures" [42, 43]. There are some suggestive clues about pathophysiological association between migraine attacks and epileptic seizures too [44–46]. Lumbar puncture is useful in determining the presence of infection or blood or increased intracranial pressure.

Primary and secondary headaches

As a general rule IHS classification system divides headache into primary and secondary headache disorders. In a primary headache disorder, headache itself is the illness and headache is not attributed to any other disorder. Primary headaches comprise migraine, tension-type headache, cluster headache, other autonomic cephalgias and other primary headache disorders. In secondary headache disorders, headache is the symptom of identifiable structural, metabolic or other abnormality. In the case of secondary headaches, special attention must be paid to symptoms of increased intracranial pressure and progressive neurological dysfunction. Red flags include the first or worst headache ever in the life, recent headache onset, increasing severity or frequency, occipital location, awakening from sleep because of headache, headache occurring exclusively in the morning associated with severe vomiting and headache associated with straining. Secondary headaches may occur in an acute (such as subarachnoid haemorrhage), subacute (such as meningitis) or progressive (such as neoplasms) fashion.

In children and adolescents, the abrupt onset of severe headache is most frequently caused by upper respiratory tract infection with fever, by sinusitis or by migraine. Serious conditions such as brain tumours or intracranial haemorrhages are uncommon and, when present, are usually accompanied by neurological signs such as papilledema, hemiparesis or ataxia [43].

Both epidemiological and clinical studies have shown that most common causes of headaches in children and adolescents are migraine and TTH.

Migraine

Migraine is a heterogeneous disorder: attacks vary in pain intensity, duration, pattern of associated features, and frequency of occurrence. Some migraineurs have recurrent attacks without remission periods; others experience symptom-free intervals lasting several years; a third group becomes free of attacks for the rest of their life [47].

Migraine is the second most common cause of chronic recurrent headache in school children. The prevalence ranges from 3.2 to 14.5% [4–6, 26, 47–49]. Positive family history for headache is commonly reported with a frequency of 60–77.5% [4, 22].

Over the last five decades, several definitions of paediatric migraine have been proposed. Vahlquist [50], followed by Bille [1], Prensky and Sommer [51] have been followed by IHS proposing a new set of criteria [52]. Revising the IHS headache duration criterion, i.e. decreasing minimum headache duration from 2 to 1 h, the utility of the IHS criteria for migraine performed 47–86.6% sensitivity and 92.4–98.6% specificity [53–56]. The currently accepted classification system for migraine was published by the International Headache Society in 2004 and is known as the International Classification of Headache Disorders (ICHD-II) [57].

Modification of ICHD-II criteria to include bilateral headache, headache duration of 1–72 h, and nausea and/or vomiting plus two of five other associated symptoms (photophobia, phonophobia, difficulty thinking, lightheadedness, or fatigue), in addition to the usual description of moderate to severe pain of a throbbing or pulsating nature worsening or limiting physical activity, improved sensitivity of migraine diagnosis to 84.4% [47, 58].

Balottin [25] demonstrated that the ICHD-II criteria are poorly applicable to children under the age of 6 years. Therefore, the development of alternative criteria might be useful [59, 60]. Further changes in ICHD-II criteria for paediatric migraine could stem from researches comparing the occurrence of headache in the family members and the prevalence of osmophobia in large samples of migraine and TTH patients. Both osmophobia and positive family history could thus become useful in better differentiating migraine and TTH. The prevalence of osmophobia during migraine attacks was 18.5%, and was higher in migraine patients (25.1%) than in those with TTH (8.3%). Osmophobia showed more specificity than phonophobia or photophobia in the differential diagnosis between migraine and TTH [25, 61].

Most migraine symptoms included in ICHD-II are not specific for the paediatric age groups. Among various migraine characteristics and associated disorders only type of migraine, migraine frequency, vomiting and dizziness were related to age [62]. Vomiting may help the diagnosis of migraine in young children with a familial history of migraine and dizziness is more common in children >11 years old and may aid the diagnostic process in this age group [62].

A bidirectional relationship between migraine and depression suggests a neurobiological link. Adverse experiences particularly childhood maltreatment, may alter neurobiological systems, and predispose to a multiplicity of adult chronic disorders. The majority of the studies with clinical populations show slightly higher scores on at least one of the anxiety or depression scales in the migraine group as compared to the control group. However, in all eleven studies, the average score on the anxiety and depression scales obtained by children with migraine did not reach a pathological level, according to the norms established by the validated scales. Findings point to above average levels of anxiety or depression, rather than diagnosed psychopathologies. Therefore, certain authors use the term "sub-clinical". None of the three studies carried out in the general population revealed differences between the anxiety and depression scores in children with migraine as opposed to children in the control group. The difference in results from studies in the general population and clinical populations can most likely be explained by a recruitment bias. Studies conducted with clinical populations recruit subjects from specialised medical consultations for children and adolescents with migraine, who are probably not representative of the general population. These results contradict those found in the adult population. More studies are needed to better clarify the links between anxiety, depression, and migraine in children, adolescents and adults. The association of childhood sexual abuse with migraine and depression is amplified if abuse also occurs at a later age [20, 34, 63–65].

To ensure the validity of future studies, the following remarks should be taken into account.

- The distinction between headache and migraine is not always clear, even when ICHD criteria are used.
- The children considered to have migraines often have a variety of diagnoses.
- Studies should only use the ICHD second edition criteria.
- Children suffering from migraine are usually recruited from specialised headache centres in hospitals. This is a very specific population and probably not representative of children with migraine in the general population.
- In contrast, studies including patients from specialised centres are relevant too, since they are reflecting the situation in those patients actually seen by physicians.

Migraine variants

Familial hemiplegic migraine (FHM)

FHM is an uncommon and genetically heterogeneous autosomal dominant subtype of migraine with aura in which the aura consists of hemiparesis. Three subtypes of FHM have been described: FHM1, FHM2 and FHM3. Mutations in the genes CACNA1A12 and SCNA1A13, encoding the pore-forming alpha-1 subunits of the neuronal voltage-gated Ca^{2+} channels and Na^{+} channels, are responsible for FHM1 and FHM3, respectively. Mutations in ATP1A2,14 encoding the alpha-2 subunit of the Na^{+}, K^{+} ATPase, are responsible for FHM2. The gene mutations for FHM are associated with phenotypes that show an overlap between migraine and other paroxysmal disorders [i.e. CACNA1A and episodic ataxia; SCNA1A and generalised epilepsy with febrile seizures plus (GEFS+)]. These findings provide compelling evidence for ion channels as key targets for preventive migraine treatment [66–69].

Basilar-type migraine

Basilar-type migraine is a migraine variant that is classified as part of the spectrum of migraine with aura in the ICHD-II classification. The diagnostic criteria comprise vertigo, visual disturbances in both hemifields, bilateral sensory symptoms and ataxia. The sudden appearance of diplopia, vertigo and vomiting must prompt consideration of disorders within the posterior fossa such as arteriovenous malformations, cavernous angiomas, tumours or congenital malformations [70–72].

Ophthalmoplegic migraine

Ophthalmoplegic migraine (OM) is one of the most clinically challenging migraine variants and, fortunately, one of the least common (annual incidence of 0.7 per million). It has been classified by the Headache Classification Committee of the International Headache Society (IHS) in 2004 under the heading of 'Cranial neuralgias and central causes of facial pain' [11, 15]. OM is defined as consisting of at least two episodes of headache accompanied or followed within 4 days of its onset by paresis of one or more of the third, fourth and/or sixth cranial nerves, with investigations having ruled out parasellar, orbital fissure and posterior fossa lesions. Contrast-enhanced magnetic resonance

imaging performed during symptomatic and postsymptomatic periods in patients with ophthalmoplegic migraine may hold great value in identifying the pathophysiological features of oculomotor nerve palsies. Of cases demonstrating abnormal magnetic resonance imaging, a majority show improved but persistent changes on repeat imaging [73–75].

Retinal migraine

Retinal migraine is extremely uncommon in children and usually seen in young adults. Unlike the descending curtain-like onset of amaurosis fugax, retinal migraine causes patients to experience brief (seconds to <60 min), sudden, monocular blackouts or "grayouts" or bright, blind episodes of visual disturbance before, after or during headache attacks [71, 76].

"Alice in Wonderland" syndrome

Originated from Lewis Carol's novel and characterised by bizarre visual illusions and spatial distortions which precede headaches. The children may describe bizarre or vivid visual illusions such as micropsia, macropsia, metamorphopsia and teleopsia [71].

Acute confusional migraine (ACM)

This rare type of migraine described as acute confusional states, lasting 4–24 h, associated with agitation and aphasia commonly seen in juvenile migraineurs. ACM may be a presenting feature and important clue, enabling CADASIL to be recognised. Therefore, a brain MRI and/or testing for Notch3 mutations should be considered in adult patients with ACM [77–79].

Migraine equivalents

Migraine equivalents of infancy, childhood, and adolescence are recognised periodic, paroxysmal syndromes without associated headache that are thought to be migrainous in aetiology. Following equivalents are presently recognised.

1. Cyclical vomiting (ICHD-II 1.3.1)
2. Abdominal migraine (ICHD-II 1.3.2)
3. Benign paroxysmal vertigo (ICHD-II 1.3.3)
4. Benign paroxysmal torticollis (ICHD-II A1.3.5)

Analgesic overuse may cause a worsening of non-cephalic pain in patients with extra-cephalic variants of migraine [57, 80].

Diagnosis of migraine

The diagnosis of migraine rests mainly on clinical criteria, thus a correct evaluation begins with a thorough medical history followed by a complete physical and neurological examination including examination of the optic fundus. Recently, a practice parameter that outlined guidelines for the clinical and laboratory evaluation of children and adolescents with recurrent headaches [71] stated that the routine use of any diagnostic studies is not indicated when the clinical history has no associated risk factors and the child's examination is normal.

Tension-type headache

Although TTH and migraine are the two most common types of headache in children and adolescents, most articles address migraine headache. The smaller genetic effect on TTH than on migraine suggests that the two disorders are distinct. However, many believe that TTH and migraine represent the same pathophysiological spectrum [81].

Prevalence

TTH was reported less common in children under 10–12 years of age and more frequent in adolescents, but with reservations for methodological differences and interpretation of results, most of the epidemiological studies found that TTH was the most frequent headache in children aged 8–12 years. The prevalence of TTH in schoolchildren has been reported as 0.9–72.8% relating to study design and psychosocial events. The prevalence of TTH increases with age [5, 13, 81–83].

Diagnosis of TTH

TTH may be hard to differentiate from migraine in children as some of the symptoms overlap. Regarding the frequency of TTH ICHD-II differentiates infrequent episodic TTH occurring less than once a month, frequent episodic TTH present on up to 14 days per month and chronic TTH occurring at least on 15 days per month or 180 days per year. TTH is characterised by a bilateral pressing tightness occurring bilaterally anywhere on cranium or suboccipital region. The pain is mild to moderate in intensity and usually not aggravated by physical activity. Associated symptoms are absent or limited to one out of photophobia and phonophobia in episodic TTH and one out of mild nausea, photophobia and phonophobia in chronic TTH [57, 81].

Stressors in TTH

Anxiety and psychological stress factors are often present and headache symptoms may be triggered by additional stressful situations [84].

Underlying psychological stress factors should be evaluated. In children, a connection seems possible between TTH and psychosocial stress, psychiatric disorders, muscular stress, or oromandibular dysfunction. Childhood TTH is associated with a higher rate of divorced parents and fewer peer relations as well as an unhappy family atmosphere. In addition, children with episodic TTH were more likely to report somatic complaints and family problems than those without headache. Children and adolescents with chronic diseases and stressful family events have an increased risk for chronic TTH. Of children with chronic TTH, over 50% have had predisposing physical or emotional stress factors. Compared to migraine group, children with TTH had greater psychological and temperamental difficulties [34, 84–87]. A headache diary is a useful method for the differentiation of headache types. The diagnosis of TTH requires exclusion of secondary headaches.

Cluster headache and other trigeminal autonomic cephalgias

Cluster headache (CH), the most painful of the primary headaches is a disorder with well-known diagnostic criteria. The condition usually begins in the second decade of life; the prevalence of childhood onset is approximately 0.1% and the sex ratio is in favour of men (M:F $\sim$3.2:1), but with a wide variation of range (1:1–6:1). Onset may be as soon as 3 years, but there is a relatively low number of cases with onset <10 years old. A suspected case in a 1-year-old infant has also been described [88–90]. There are relatively few reports on the prevalence and clinical features in CH in children and adolescents, since only few population studies have also considered the paediatric population [88, 91, 92].

Paroxysmal hemicrania is a rare headache with a prevalence of 0.02%. Paroxysmal hemicrania generally begins in adulthood with onset generally after the third decade of life. Characterised by brief, unilateral attacks of intense pain around the supraorbital and temporal region, afflicted patients may have from usually 5–6 to as many as 30 attacks per day that last from 2 to 45 min. Like other trigeminal autonomic cephalgias, paroxysmal hemicrania is associated with autonomic symptoms. A key element defining paroxysmal hemicranias is their exquisite sensitivity to indomethacin. Relatively few paediatric cases have been reported in the literature. Children as young as 3 years of age have been described with the disorder [93–95].

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) is an extremely rare disorder in childhood with only few cases reported in the literature Unlike paroxysmal hemicrania, SUNCT syndrome is unresponsive to indomethacin, and neither oxygen nor other non-steroidal anti-inflammatory drugs provide relief [93, 96].

Chronic headache

Chronic headache is frequently seen in children and adolescents. ICHD-II provides separate definitions for the chronic forms of migraine, tension-type headache, cluster headache, paroxysmal hemicrania and several secondary headaches. In addition there are primary and secondary headaches which are chronic per se, most importantly medication overuse headache. In ICHD-II, the definition of "chronicity" is heterogeneous. In migraine, TTH or medication overuse headache, it is defined by headaches present on 15 or more days per month for at least 3 months, whereas different chronicity in CH or paroxysmal hemicrania refers to the lack of remission periods [50].

In contrast to ICHD-II, the term chronic daily headache (CDH, with or without differentiating the specific ICHD subtype) is frequently used in the literature. Being aware of this heterogeneity of definitions we did not exclude studies referring to CDH from this review. Chronic headache is estimated to occur in up to 5% of adults and is the most common headache type reported in headache clinics. In children and adolescents, chronic headache is an exceptionally challenging type of headache to treat. The most important subtypes are chronic migraine (CM), chronic tension-type headache (CTTH) and new daily persistent headache (NDPH) [97]. Chronic headache has different expressions in children and adults; the different expressions may reflect several different aetiologies or a developmental continuum. Although a positive family history predisposes children to develop headache, many environmental, biological and psychological processes may share a role in the aetiology [98, 99].

Comorbid chronic migraine and CTTH was the most frequent subtype of CDH (53%). Stressors that precipitated or contributed to the maintenance of CDH were judged important in 63% of the sufferers. Psychiatric disorders are notable in CDH (about 64% of patients) and predict (mainly anxiety) a poorer outcome. Physical abuse (10% vs. 0, $p = 0.012$) and parental divorce (17% vs. 3%, odds ratio = 5.8, $p = 0.015$) were more frequent in the CDH group. The results indicate that childhood adversities may

contribute to greater risk of the development of CDH in young adolescents [100–102].

NDPH is the least studied form of CDH. Most adolescents with NDPH do not overuse acute medication and most have prominent migraine features. Therefore, diagnostic criteria should require abrupt onset of a primary CDH of long duration as the sole requirement for NDPH diagnosis [99].

Other primary headaches

These types of headaches are very rare in childhood and adolescent practice. Some of them are responsive to adequate doses of indomethacin. Before the diagnosis of benign primary headache disorders symptomatic causes (the "crowded" posterior fossa, brain tumours, Chiari malformation, syringobulbia and vascular malformations) should be excluded [103].

Secondary headaches

Secondary headaches are also called "organic headaches" by some clinicians. These headaches can be grouped in three different ways: aetiology, symptom complex and temporal presentation [104]. Chronic headache in childhood is rarely due to serious intracranial pathology. Some of the important causes of secondary headache disorders are follows.

- Trauma
- Vascular disorders
- Hydrocephalus and neoplasms
- Substance use
- Intracranial infections
- Metabolic disorders and hypoxia
- Disorders of cranium (e.g. sinuses, eyes, etc.).
- Epileptic disorders (both of ictal epileptic headache and differential diagnosis from other benign focal idiopathic epilepsy of infancy).

Some important clues about secondary headache disorders can be summarised as follows

- Careful history-taking and thorough clinical examination will identify patients with serious underlying brain abnormalities. A change in headache symptomatology or personality should lower the threshold for imaging. However, there is no role for routine neuroimaging in the management of children with primary headache disorders [104–110].
- Headaches occurring soon after trauma frequently involve loss of consciousness, post-traumatic amnesia, or abnormal neurological symptoms and signs, post-traumatic headaches should be kept in mind.
- Minor head trauma could trigger primary headaches (especially migraine) in young children.
- Vascular disorders including vasculitis, hypertension, thrombosis, emboli, and haemorrhage, the latter being secondary to aneurysms, vascular malformations, and trauma are rare, but life-threatening causes of headaches in children and adolescents.
- In progressive headaches associated with signs of increased intracranial pressure, hydrocephalus, idiopathic intracranial hypertension and intracranial hypertension secondary to metabolic, toxic and hormonal causes should be considered.
- Intracranial tumours are the second most common type of neoplasm in children. Symptoms are often unspecific, depending not only on the localization of the tumour, but also on the age of the child. In the majority of patients, the neurological examination will be abnormal, and diagnosis should be confirmed by neuroimaging. It also should be kept in mind that non-neoplastic mass lesions may present in a similar fashion.
- In children presenting with fever, rash, lethargy, irritability, a bulging fontanel, neck stiffness, mental status changes, and/or focal neurological abnormalities intracranial infections should be kept in mind.
- Headaches are seen in patients with medication overuse and use of substances such cocaine, narcotics and amphetamines with or without associated neurological and autonomic symptoms.
- Among headache associated conscious disturbances epileptic disorders should be kept in mind.
- Compound and mixed types of astigmatism, anisometropia and miscorrection of refractive error are found more often in patients with headache than in control subjects.
- Acute sinusitis often presents with fever, rhinorrhea and tenderness over the facial area, as well as headaches. Although the 25% of patient who have been diagnosed as sinusitis previously had at least one sinusitis related complaint, this finding does not seem to be important, because 60% of the patients do not report improvement after sinusitis treatment.
- Misdiagnosis of primary headache disorders should be kept in mind.

Conclusions

- Headache in children and adolescent is a growing problem possibly related to changing lifestyle and stressors.
- Families and physicians need more knowledge about headaches in children and adolescents.

- Headache diagnosis may be more difficult in these age groups due to declaration problems and overlapping symptoms.
- In each visit of a subject with a primary headache disorders a secondary cause of headache should be kept in mind.
- Headache evaluation should be including cognitive functions and impact on daily living activities.
- Comorbidities must be considered.
- Headache diary is a mandatory tool for diagnosis and effective follow-up in patients with recurrent headaches.
- Children with headache are more likely to experience psychosocial adversity and to grow up with an excess of both headache and other physical and psychiatric symptoms and this creates an important healthcare problem for their future life.

Taking careful history from a patient presenting with headache is the prerequisite for further diagnostic and therapeutic management.

Conflict of interest None.

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REVIEW ARTICLE

Migraine and psychiatric comorbidity: a review of clinical findings

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Abstract Migraine is an extremely common disorder. The underlying mechanisms of this chronic illness interspersed with acute symptoms appear to be increasingly complex. An important aspect of migraine heterogeneity is comorbidity with other neurological diseases, cardiovascular disorders, and psychiatric illnesses. Depressive disorders are among the leading causes of disability worldwide according to WHO estimation. In this review, we have mainly considered the findings from general population studies and studies on clinical samples, in adults and children, focusing on the association between migraine and psychiatric disorders (axis I of the DSM), carried over after the first classification of IHS (1988). Though not easily comparable due to differences in methodology to reach diagnosis, general population studies generally indicate an increased risk of affective and anxiety disorders in patients with migraine, compared to non-migrainous subjects. There would also be a trend towards an association of migraine with bipolar disorder, but not with substance abuse/dependence. With respect to migraine subtypes, comorbidity mainly involves migraine with aura. Patients suffering from migraine, however, show a decreased risk of developing affective and anxiety disorders compared to patients with daily chronic headache. It would also appear that psychiatric disorders prevail in patients with chronic headache and substance use than in patients with simple migraine. The mechanisms underlying migraine psychiatric comorbidity are presently poorly understood, but this topic remains a priority for future research. Psychiatric comorbidity indeed affects migraine evolution, may lead to chronic substance use, and may change treatment strategies, eventually modifying the outcome of this important disorder.

Keywords Migraine · Comorbidity · Psychiatric disorders · Depression · Meta-analysis

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Introduction

Migraine is an extremely common disorder, characterized by the recurrence of painful and non-painful episodic phenomena and a variety of neurological manifestations. Nosographically, it is thus a chronic illness (migraine seen as a "disease") interspersed with acute signs and symptoms (migraine seen as an "attack"). The mechanisms underlying migraine appear to be increasingly complicated, and the term complex disease is used to define the nature of the

illness and to describe the whole breadth of the clinical and subclinical aspects that it encompasses [1, 2]. The wide heterogeneity of migraine accounts for the observation that the large population of migraine sufferers includes patients living an almost normal life and patients complaining of serious disability, i.e. facing social, affective and occupational limitations [3].

While genetic determinants are certainly at the basis of some (and probably all) clinical forms, the contribution of biological factors critically affects the clinical appearance of migraine. Recent findings in the field of neurogenetics have altered deeply our approach to migraine, emphasising the limits of the current diagnostic and nosographic system. With the current diagnostic criteria of International Headache Society (IHS) [4] allowing a better phenotypical characterisation of patients, the importance of the role of genetics in the mechanisms of migraine is increasing. In most cases, however, migraine occurs as multifactorial inherited character. Therefore, different genes or loci may interact with factors intrinsic to the individual (e.g. the hormone milieu) and/or with exogenous factors (e.g. psychosocial stressors related to the family or to the working environment, geoclimatic changes, food), generating different clinical forms of the disease [5].

Another important aspect of migraine heterogeneity, in close proximity to the field of genetic determinants, is the significant association between migraine and other neurological diseases (such as epilepsy, cerebrovascular disorders and stroke, mitochondrial diseases), cardiovascular disorders (arterial hypertension, mitral valve prolapse), and particularly psychiatric illnesses (anxiety, affective and personality disorders) [6]. This non-coincidental association of two or more diseases, referred to as comorbidity, may result from different mutations in the same gene (allelic disease) or mutations in genes located in neighbouring segments of the same chromosome.

A further aspect of migraine heterogeneity, extremely relevant to clinical research, is that the phenotypical expression of comorbidity may vary over time. This emerges upon simple observation of the natural history of migraine in the lifetime of different individuals. The phenotypical manifestations remain unchanged over the years in some patients, while in others the clinical picture becomes more complicated, and may include arterial hypertension (per se a risk factor for cerebrovascular accidents) and/or anxiety and mood disturbances. On the other hand, the presence of hypertension and psychiatric disorders often facilitates changes in the migraine pattern, resulting in forms of daily headache now referred to as chronic migraine [7].

It would therefore appear that the clinical-descriptive approach to the patient, demanded by the current diagnostic criteria, allows only a partial understanding of migraine, the nature of which certainly appears to be more complex and heterogeneous than previously thought.

Migraine psychiatric comorbidity

The relationship between migraine and certain psychological features, such as a tendency toward perfectionism, neuroticism, repressed aggressivity and melancholic mood has been repeatedly reported for more than a century. Over the years, several data in the literature have been collected on anedoctical bases. Recently, with the development of new diagnostic criteria and statistical methodology, some of these observations have been confirmed [8, 9], but it is impossible to compare across all previous investigations due to differences in nosography and case definition. For instance, earlier than 2004, some nosologic entities, such as chronic migraine, which is frequently comorbid with psychiatric disorders, were not defined by diagnostic criteria.

Understanding the psychiatric correlates of migraine is critical for several reasons. Depressive disorders are among the leading causes of disability worldwide [10] and the WHO estimates that major depressive disorder will become the second leading cause of disease burden by the year 2020, second only to ischemic heart disease [11]. Migraine is a public health problem with an enormous impact on both the individual sufferer and on society. It is per se the most burdensome of the primary headache disorders [12, 13]. The presence of psychiatric conditions is a risk factor for transformation of migraine into a chronic form [7]. Furthermore, individuals with migraine and comorbid psychiatric disorders are greater health resources users than migraineurs without psychiatric conditions. Recognizing this comorbidity should therefore result in improved patient management, via first-line treatment targeted at both conditions.

In this review, we have mainly considered the studies carried over after the publication of the first classification of the IHS [14], in adults and children, focused on the association between migraine and psychiatric disorders, as defined on axis I of the Diagnostic and Statistical Manual of Mental Disorders (DSM) [15].

General population studies

Since the first introduction of the IHS criteria [14], several studies of community-drawn samples have examined migraine psychiatric comorbidity. All cross-sectional investigations of psychiatric disorder prevalence in ‘migraine’ compared with ‘non-migraine’ samples found an increased risk of anxiety disorders, particularly panic

disorder (PD) and phobias. As for other anxiety syndromes, one study [16] found an association between migraine and obsessive–compulsive disorder (OCD) as well as generalized anxiety disorder (GAD), but these associations were not replicated in subsequent investigations [17–19]. All these investigations were of high methodological quality (including rigorous sampling criteria in a community setting, use of structured interviews and application of DSM diagnostic criteria). The reasons for this discrepancy therefore remain uncertain.

Previous investigations of mood disorders have been highly consistent in reporting an increased prevalence of major depressive disorder (MDD) in patients with migraine [6]. The only one discrepant study [20] was characterized by several methodological differences and limitations that may account for the lack of any association between MDD and migraine. First, the patients studied were of considerably younger age and were not sex-matched by gender. Second, the sample was not enough representative of the general population or of clinical settings, since the study group included young adults selected for 'high psychopathological risk' as detected by a general symptom scale. Finally, the recruitment of the clinical cases was based on the use of a structured diagnostic interview (SPIKE) originally designed for epidemiological studies and not specifically for psychiatric diagnostic purposes. An increased risk of current depression in migraine patients was also reported in a community-based study [21]. This investigation included an assessment of quality of life, and the conclusions of the authors were that both migraine and depressive disturbances exert a significant but independent impact on this parameter. Furthermore, in another study in patients over 65 years, the risk of current depression was found to be increased in migraine patients compared to healthy controls [22] and headache appeared to be independently associated with depression in the elderly. However, the diagnostic instruments in this setting included scales not specifically intended for the assessment of DSM criteria. Further evidence of a high prevalence of depressive symptoms in adult to elderly patients with migraine was provided by a recent cross-sectional study [23].

In patients with migraine with aura, an association was early reported with suicide attempts, even after adjustment of data for major depression [16]. This observation is in line with later studies by the same group claiming that migraine with aura is characterized by psychiatric comorbidity more frequently than migraine without aura [24]. Interestingly, similar findings were recently obtained in a sample of adolescents aged 13–15 years. A higher frequency of suicidal ideation was observed in younger adolescents with migraine with aura or with high frequency of attacks, these associations being independent of depressive symptoms [25].

With regard to other forms of affective disorder, in one of the studies [16] only migraine with aura was found to be significantly associated with bipolar disorder (BD). Later observations did not confirm this association, but they did not distinguish between migraine subtypes [17]. Recently, a significant association between migraine and BD was reported by one study [18], with migraine subjects showing BD twice as often as those without migraine. Results were further confirmed by a subsequent, large study in a population-based sample [19].

In cross-sectional investigations, substance-related disorders have been examined in a few cases. An increased risk of alcohol and drug abuse was reported in migraine sufferers [16], but subsequent studies could not replicate this finding [20]. One possible explanation for such discrepancy may be related to the fact that BD and substance abuse are highly comorbid. However, more recent studies have shown again no association between migraine and drug, alcohol or substance abuse/dependence [18, 19].

The prospective analyses carried over in almost all the mentioned studies were also addressed to measure the risk of psychiatric disorders in subjects primarily suffering from migraine. For instance, the risk of panic disorder and phobia onset during the follow-up period was found to be greater for patients with migraine than for those without migraine [26]. However, in this study, no clear significant association was reported between migraine and affective disorders, at variance with other authors [28], possibly due to the different headache diagnostic criteria used. In a study following patients for up to 15 years, the presence of phobia at the basal evaluation was also shown to predict the subsequent occurrence of migraine [17]. Recently, Ratcliffe et al. [19] examined for the first time the relationship between physician-diagnosed migraine and multiple psychiatric disorders in a large, nationally representative sample. Important points overcoming the limitations of previous studies were the use of a standardized interview (Composite International Diagnostic Interview, CIDI) and the fact that physical health problems were directly diagnosed by a physician and not reported by patients. Past-year migraine was found to be associated with depression, dysthymia, bipolar disorder, panic attacks, panic disorder, agoraphobia and simple phobia.

Interestingly, a recent study investigated the presence of migraine with and without aura, probable migraine and no migraine, according to the IHS criteria, in a large sample of concordantly depressed sibling pairs [29]. The findings supported the hypothesis that the two forms of migraine are different, migraine with aura representing the extreme end of a continuum of migraine familial liability, even in a defined psychiatric population (i.e. depressed patients). Accordingly, in a case–control study, it was recently observed that not only there is a general relationship

between recurrent headache and depression, but also a specific association between depression and migraine with aura [30].

Studies on clinical samples

Since the introduction of the IHS criteria (1988) [14], several investigations have been carried over in clinic-drawn samples, with the aim of comparing migraine with other forms of headache (tension type headache, chronic daily headache, transformed migraine, and daily headaches with chronic substance abuse). None of the studies comparing migraine and tension-type headache could find significant differences in terms of psychiatric comorbidity [31–33], whereas the risk of psychiatric disorders was found to be increased in chronic headache, and particularly transformed migraine, as compared to episodic migraine patients [33–36]. In particular, a study by our group [34] investigated comorbidity with anxiety and depression in several groups of patients, including low back pain patients. While extrapolations of findings should be done cautiously (due to the fact that patients suffering from migraine with interval headache and patients with chronic tension type headache were considered as a whole sample), a significant comorbidity was observed in all groups of patients. Comorbidity was even more pronounced in patients who had had chronic headache for more than 5 years than in those with shorter disease duration. Interestingly, in this study all psychiatric disorders except for somatoform disorders were found to be associated with headache, suggesting that psychiatric comorbidity may be confined and specific to headache category, and it is not merely accounted for by the coexistence of chronic pain. Another study [33] compared migraine sufferers with daily headache patients with chronic substance abuse, and found that major depression was twice as frequent in patients with analgesic abuse. Similarly, other authors [35] demonstrated an increased risk of major depression, panic disorder and social phobia in patients with transformed migraine and chronic substance use, even after adjustment for age and gender. Juang et al. [36] compared patients suffering from transformed migraine with those suffering from chronic tension-type headache, and found a higher frequency of anxiety in transformed migraine patients after adjustment for age and gender. However, similar to the other studies in the field, the role of the diagnostic criteria for substance abuse or dependence criteria was not critically considered. Other authors [37] found that patients with migraine show higher severity of somatic, depressive and anxiety complaints. In addition, migraine appeared to be the strongest independent factor in predicting somatic severity of major depressive disorder, even after controlling for anxiety comorbidities and demographic variables. Recently, in a cross-sectional study panic disorder was found to prevail in migraine compared with tension-type headache or migraine plus tension-type headache, and the association was stronger when migraine was compared to pure tension-type headache; similarly, obsessive–complulsive disorder was more closely associated with migraine than to tension-type headache [38]. The importance of the impact of psychiatric comorbidity on chronicity and impaired quality of life in chronic daily headache sufferers has been pointed out by a recent selective overview [39]. In particular, the complex interplay of factors underlying the relationship between migraine, suicide risk and mood disorders deserve scientific interest and better methododologically based investigation [40].

From children to grown-up

The hypothesis of a relationship between migraine and psychiatric disorders beginning with anxiety in childhood and adolescence, followed by migraine and later depression [16, 20, 26, 27] pointed the attention on the role of pediatric age.

As previously reported, the presence of psychiatric disorders is more related to severity and frequency of non-migrainous headache than to migraine [24]. The higher prevalence of comorbid psychiatric disorders in chronic daily headache than other headache subtypes both in children/adolescents and adults further supports this finding [41]. The burden of childhood adversities on chronic daily headache did not differ between chronic migraine and chronic tension-type headache in a population study [11].

It has been hypothesized that chronic illness in general, rather than a specific disorder, explains variations in psychological functioning between chronically ill and healthy children. This to stress that psychiatric disorders may not specifically relate to migraine per se, but to migraine as a kind of disabling and recurrent pain. Cunningham [42], comparing migraine and chronic non-headache pain samples, found no difference in anxiety and depression levels between the two groups with chronic pain, with respect to pain-free controls. It is noteworthy that studies looking for differences between migraine and other headache subtypes did not find specific psychological characteristics between migraineurs and tension-type headache sufferers [32, 43]. Recently, a study comparing headache patients and patients with recurrent abdominal pain did not find differences by the psychological point of view (internalizing vs. externalizing disorders) [44]. This suggests that in pediatric age the role of psychological factors might be more related to the frequency and severity of headaches, than to sole migraine. Recently, a population based study on 13–15 year

adolescents found an increased risk of suicidal ideation among those with migraine with aura and high frequency non-migrainous headache; the risk increased with increasing frequency of attacks [25].

From the psychiatric point of view, studies consider often "headaches" and/or "abdominal pain" as somatic complaints that are symptoms of child or adolescent psychopathology. Livingston et al. [45] found that between 25 and 30% of children admitted to a psychiatric hospital had physical symptoms, including headache, food intolerance, abdominal pain, nausea and dizziness. Different interpretations have been suggested by other studies. Andrasik et al. [46] found a greater number of somatic complaints in migraineurs and higher ratings of depression and anxiety among migrainous adolescents, compared to matched headache-free subjects. The suggested hypothesis was that "frequent, unexplainable and intense head pain would likely lead to heightened levels of depression and anxiety". Another aspect to be borne in mind is the presence of subclinical conditions, such as in patients without defined psychopathology but with psychological distress following life-events (e.g. parental divorce) or personality characteristics (e.g. tendency to perfectionism), aspects that may contribute to trigger headache. The diagnostic workup of headache in children and adolescents should always include a psychological assessment for a complete framing of the clinical condition. A recent clinical study [47] showed a connection between childhood maltreatments, adult chronic and/or severe migraine and major depression: migraineurs with current depression reported more frequent physical and sexual abuse compared to those without depression; women with major depression were more likely to report sexual abuse occurring before 12 years, and the relationship was stronger when abuse occurred both before and after 12 years; women with migraine and depression were four times more likely to have a history of some type of childhood maltreatment. These findings outline the interface existing between neurology and psychiatry, organic and psychological, and likely genetic and environmental factors linked to migraine.

A study in a psychiatric setting [48] also showed that headache is the most frequent somatic symptom in children and adolescents referred for emotional and behavioural disorders, as well as in patients with depression and/or anxiety. With regard to gender differences, females appear to be more affected. A population, prospective cohort study on headache adolescents [49] showed gender differences in comorbid associations, with allergy, bronchial asthma, diabetes mellitus and stomach-ache more common in boys, and psychiatric symptoms and sleep disturbances in girls. A 1-year longitudinal study in adolescent headache sufferers [50] found depression, insomnia and low self-esteem associated to headache occurrence, and a likely temporal trend was suggested, with depression and low self-esteem preceding headache onset, even if only in girls. However, the study did not apply ICHD criteria and other standardized (DSM-IV or ICD-10) diagnostic criteria (e.g. it was unclear whether or not low self-esteem or insomnia were related to depression itself). A more recent study [51] showed an increased risk for females of reporting higher levels of depression (and anxiety), and an elevated risk of developing chronic daily headache and medication overuse when patients showed psychiatric disorders as well. The negative effect of the presence of psychiatric disorders in general and depression in particular on the outcome is not new in literature [41, 52], and was recently confirmed in a population based study, including a 2-year follow-up [53].

Similarly to migraine, psychiatric disorders run in families [20]. Anxiety and mood disorders are particularly frequent in migraineurs and their relatives [20]. A recent study [53] showed that psychiatric disorders are equally represented in migraine and other headache subtypes. Noteworthy, parents of migraine children showed a significant higher comorbidity with psychiatric disorders than parents of children with other headache subtypes. This aspect requires attention, because it is the first point clearly differentiating migraineurs from other headache patients, even if further studies are required to support this finding. Migraine children seem to be characterized by a higher prevalence of headache familial recurrence and psychiatric disorders in parents, than other headache subtypes [54]. Both psychiatric comorbidity and headache familial recurrence are also very frequent in children with other headaches, but they can occur together or alone. This pattern of results suggests that anxiety/depression and headache familial recurrence act as additive factors in non-migrainous headaches, while in migraine they might represent, together with psychiatric disorders in parents, interrelated aspects of a more complex relationship. This means that the higher the weight of headache familial recurrence the higher the possibility that children show psychiatric comorbidity, but only in the case of migraine.

In most part of the studies in children and adolescents with migraine, the association with anxiety (and mood) disorders appears to be an important topic, even though a recent systematic review suggested overall inconclusive evidence on this matter [55]. The presence of depression is associated with a poor outcome for any headache subtype. Females have an increased risk for any of the above items. Whether the association is specifically linked to recurrent headache or to headache as a chronic pain is unclear. Moreover, we do not know exactly what happens in children, because depression in children has specific clinical symptoms that complicate its recognition and diagnosis, so that studies might have underreported or misdiagnosed it. The aetiology of the comorbid association is also unclear,

and there are no studies on pharmacological and/or non-pharmacological treatment of the comorbid disorders due to the young age. Like in adults, further studies based on proper assessment tools and fulfilling the international systems of classification of both headache and mood disorders are required.

Metanalysis of studies investigating the association of migraine and depression

With particular regard to the most investigated psychiatric comorbidity, i.e. depression, the crucial issue is whether depression is more frequent in individuals with headache and particularly with migraine and vice versa. An answer to this question may arise from studies that investigated the occurrence of these two disorders in the same population. The most reliable design of study to provide evidence on the association of the two diseases and on its nature is the cohort study. This study method consists of the analysis of the occurrence during time of depression in person with headache without depression and in normal non-depressed populations. The strategy for investigating the relationship between the two diseases may obviously be reversed looking for the occurrence of headache in depressed persons without headache. Less convincing evidence on the existence of an association between the two diseases is derived from cross-sectional studies where the temporal sequence of occurrence, and possible cause–effect relationship, are more hardly recognized. Another study design for investigating the association of two diseases is the case–control study. In case–control studies, a group of subjects with the disease of interest (cases) is compared with a group of subjects without the disease of interest (controls). This type of study needs accurate study designs in order to control for possible bias due to the effect of confounders.

Using as key words headache or migraine and depression, we retrieved in medline 47 studies on the issue of the relationship between headache and depression. Most are cross-sectional, a minority are case–control studies; no cohort studies have been retrieved. Three criteria have been used in the selection of the papers for the metanalysis. The first was the consistence of the paper content with the issue of interest. The second was the presentation of original data. The third was the possibility of deriving crude data from the paper, and this was a *conditio sine qua non* for the execution of the metanalytic procedure. Of the 47 studies, 17 were inconsistent with the issue of the relationship between migraine and depression; 5 were reviews or editorials presenting no original data; finally, for 13 studies it was impossible to derive the crude data. 12 studies remained therefore available for the metanalysis (Table 1) [7, 19, 23–25, 27, 56–60].

Table 1 shows the prevalences and the odds ratios of depression in patients with migraine with respect to

Table 1 Prevalences and odds ratios of depression in migraineurs with respect to subjects without migraine for each one of the 12 considered studies

Study	Subject age range (years)	Diagnostic tool	Without migraine Depression		With migraine Depression		OR (95% CI)
			No	Yes (%)	No	Yes (%)	
Ratcliffe et al. [19]	18–65	CIDI	3,762	305 (7.5)	455	79 (14.8)	2.1 (2.1–1.7)
Hung et al. [37]	ND	HAMD–S DSSS	62	20 (24.4)	38	35 (47.9)	2.8 (2.9–1.5)
Jette et al. [18]	15–over 65	CIDI	31,772	1,122 (3.4)	3,641	343 (8.6)	1.8 (1.8–1.6)
Camarda et al. [23]	ND	CES-D	1,043	242 (18.8)	80	71 (47.0)	3.8 (3.8–2.7)
Merikangas et al. [27]	27–28	SPIKE	367	29 (7.3)	52	9 (14.7)	2.2 (1.0–4.8)
Breslau et al. [56]	25–55	CIDI	453	86 (16.0)	287	209 (42.1)	3.8 (2.9–5.1)
Samaan et al. [30]	19–85	SCAN, BDI	808	1,070 (57.0)	43	189 (81.5)	3.3 (2.4–4.6)
Lipton et al. [21]	18–65	PRIME-MD	315	64 (16.9)	206	183 (47)	4.4 (3.2–6.0)
Lanteri-Minet et al. [58]	ND	HADS	6,651	1,264 (15.7)	1,465	442 (23.2)	1.6 (1.4–1.8)
Breslau et al. [24]	25–55	CIDI	492	94 (16.0)	318	218 (40.7)	3.6 (2.7–4.7)
Kececi et al. [59]	Over 18	DSM-IV	682	102 (13.0)	110	53 (32.5)	3.2 (2.2–4.7)
McWilliams et al. [60]	25–74	CIDI-SF	1,319	185 (18.5)	243	97 (28.5)	2.8 (2.2–3.7)
							2.2 (2.0–2.3)

HAMDS Somatic items of the Hamilton Depression Rating Scale, *DSSS* Depression and Somatic Symptoms Scale, *CES-D* Center for Epidemiologic Studies Depression Scale, *HADS* Hospital Anxiety and Depression Scale, *SCAN* Schedule for Clinical Assessment in Neuropsychiatry, *BDI* Beck Depression Inventory, *CIDI (SF)* Composite International Diagnostic Interview (Short Form), *SPIKE* Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology, *PRIME-MD* Primary Care Evaluation of Mental Disorders

subjects without migraine for each one of the 12 considered studies. Across the studies, the prevalence estimates of depression were highly variable, whereas the ratio of depression prevalence between subjects with and without migraine was more consistent. The prevalence estimates varied from a minimum of 3.4% to a maximum of 24.4% in individuals without migraine. The corresponding figures among migraineurs were 8.6 and 47.9%. The individual study odd ratios had a minimum of 1.8 and a maximum of 4.4; however, the confidence limits of each study were comprehensive of almost all the point estimates of the other studies. The overall risk estimate gave an odd of depression for people with migraine with respect to people without migraine of 2.2, with a 95% confidence interval of 2.0–2.3. It should be noted that the two largest studies [18, 56] reported the lowest odd ratios (1.6, 1.8, respectively). Furthermore, these two studies were characterized by high number of participants and this may have influenced the results and decreasing the mean values of the overall studies (Table 1).

In conclusion, all the individual studies and the overall metanalytic investigation show that depression is almost two time more frequent in subjects with migraine than in people unaffected by headache.

Mechanisms of migraine psychiatric comorbidity

Comorbidity between migraine and psychiatric disorders has been extensively studied, but the mechanisms underlying this phenomenon are far from clear. Direct and indirect data mainly stem from longitudinal studies investigating the order of onset of each condition, the changes in severity/evolution of one disorder if another is present, and the co-transmission of these disorders within families. The possible mechanisms of comorbidity are several [61]. The association of two disorders may be a result of chance. One disorder may cause another disorder (such as diabetes causes diabetic neuropathy). Shared environmental risk factors may underlie both disorders (such as head trauma causing both post-traumatic headache and post-traumatic seizures). Finally, genetic or environmental risk factors may produce a brain state resulting in both conditions. In the latter case, common neurobiological determinants may account for both disorders, and this mechanism appears to be the most appropriate for comorbidity of migraine and depression. Following this conceptual view, the evidence from literature [6, 60, 61] thus points to three main potential mechanisms, as follows:

1. psychiatric disorders are causal factors in the development of migraine. In this case, psychiatric disturbances are responsible for a full expression of migraine, and under particular circumstances for the evolution of migraine in a daily pattern (chronic migraine)
2. migraine is a causal factor in the development of psychiatric disorders. In this case, the repetition of intense and/or long lasting pain episodes may facilitate the development of anticipatory anxiety and/or depression
3. shared aetiological factors and common determinants explain the co-occurrence of both entities. In this case, there is no clear causal association, and a common substrate (e.g., deranged activity of neurotransmitters or receptors) may cause both migraine and the comorbid psychiatric disorder.

With particular regard to the relationship between the frequency of psychiatric comorbidity and the severity of migraine, some evidence [33] suggested that there is a significant association between frequency and duration of the attacks, but not with the intensity of pain. A correlation was subsequently observed between the evolution of headache and the presence of anxiety or depression. In this respect, several studies have been focused about onset of specific disorders. In one study [28], anxiety was shown to precede migraine in most patients, which in turn preceded depression. These findings were very similar to those obtained by other authors [17, 27], indicating that the onset of anxiety preceded that of migraine, which in turn preceded that of depression in most patients, and that the ages of onset of each disorder were significantly correlated.

With the aim of elucidating the role of psychiatric disorders as possible risk factors for the onset of migraine, some authors [17] showed that only the anamnestic presence of phobic disorder was predictive of the onset of migraine, at variance with that of affective disorders. The latter observation is consistent with other reports [17, 27, 28], strongly suggesting that depression and dysthymia are not risk factors for the onset of migraine.

Other studies have investigated the reciprocal relationship of migraine and psychiatric disorders. The risk of onset of depression or panic disorder during a follow-up period of over 1 year was found to be slightly greater in subjects with a history of migraine (15.5%) than in subjects with current migraine (13%) [28]. Recently, using a complex statistical hazard model, the same authors [24, 63] found no preferential order of onset for depression or panic relative to migraine, although a trend towards an order of onset of major depressive episodes in relation to severe non-migraine headache was observed. All these findings thus support the view that the comorbid disorders are bidirectionally linked. In this regard, a follow-up study in

children showed that anxiety predicted the persistence of headache in both migraine and tension-type headache patients [32].

It would therefore appear that only phobic disorders predict the onset of migraine, and that a clear bidirectional relationship exists between migraine and depression or panic disorder, that is, each disorder may represent a risk factor of the other.

Comorbidity can be alternatively explained by the hypothesis that common genetic and/or environmental risk factors may underlie both migraine and psychiatric disorders. One of the earliest reports [65], was inconclusive in this respect, though IHS criteria were not yet available. By duly applying IHS criteria, it was later found that there was indeed no familial crosstransmission between migraine and affective or anxiety disorders [20]. In another report, the risk of bipolar disorder was not increased in the relatives of non-bipolar migraine patients [66]. Taken together, these studies did not support the view that depressive and bipolar disorders share common genetic determinants with migraine. However, everyday experience indicates that in both migraine and affective disorders the frequency of episodes can increase with time, and that both disorders can progress to more chronic states with poor recovery between episodes and development of drug resistance. This suggests that sensitization phenomena may underlie both disorders [67].

Biologically based studies have also tried to address the issue of migraine psychiatric comorbidity. An association was reported between a particular dopamine D2 receptor genotype and comorbid migraine with aura, major depression and generalized anxiety disorder [68]. A lifetime history of major depression was reported to be associated with reduced tyramine conjugation (a marker of endogenous depression) in migraine patients compared with controls [69]. This observation argues against the hypothesis that depression may develop as a psychological reaction to migraine attacks. Serotonin receptors and transporters, and catecholamines have also been implicated in migraine as well as various psychiatric disorders [5, 70], and there is evidence supporting the effectiveness of several antidepressants (including SSRI abd SNRI) in the prevention or treatment of migraine [71]. Female migraineurs often experience attacks associated with falling estrogen levels around menses, and mood disturbances in women often coincide with menses, as well as the postpartum period and the perimenopausal period. Ovarian hormones, modulating numerous neurotransmitters, therefore appear to play an important role in migraine as well as in depression [72]. However, the neurobiological mechanisms of migraine psychiatric comorbidity are still far from being clear.

Impact of psychiatric comorbidity on migraine

Comorbidity with psychiatric disorders raises the global burden of migraine. Increasing evidence suggests that migraine in comorbidity with psychiatric disorders is associated with poorer health-related outcomes [18]. Several studies have so far examined health-related outcomes of migraine, investigating variables such as disability, restriction of activity, quality-of-life or mental health care utilization [73–76]. In these cases, however, investigation was regularly restricted to migraine, without taking into consideration any possible psychiatric comorbidities. When comorbidity was taken into account, in patients suffering from both conditions the prevalence of disability, restriction of activities, poorer quality of life and mental health care use was found to be higher than in those with only one of the two conditions, and even higher than in those with neither condition [18]. Other authors [77] reported that male patients with comorbid bipolar disorder and migraine were more likely than those without migraine to utilize mental health care services. The same group found that bipolar females with comorbid migraine were more likely to require assistance in their daily routine when compared with bipolar females without migraine. Patients with migraine were found more likely to have a history of various psychiatric disorders and concomitantly to report job absenteeism, to rate their general health as fair or poor, and to use mental health services [28]. Recent evidence from large populations of patients has confirmed that single-item scales are valid and reliable to assess symptom severity, psychosocial function, and quality of life [78]. Health-related quality of life was reported to be generally lower in patients with comorbid migraine and one mental health disorder [21, 63, 74]. Similarly, in patients with MDD, the coexistence of migraine was shown to predict a significant negative impact on all physical subscales and vitality in the assessment of quality of life [79]. The same group reported that subjects with migraine, anxiety, or chronic depression had higher depression scores and poor quality of life; in addition migraine, specific phobia, and panic disorder were important and independent comorbidities predicting quality of life [80]. The presence of migraine should therefore be considered as an important clinical symptom in all clinic-based samples of depressed patients. However, as already pointed out [18] the currently available studies does not elucidate whether health-related outcome variables are specific to migraine or to mental disorders [18]. Different mechanisms may link migraine, psychiatric disturbances and poor quality of life. In patients with migraine and comorbid psychiatric problems, the impairment in quality of life may indeed mirror a real ill

condition, or an altered perception of life circumstances, or both. Prospective studies will probably help to clarify these important points.

Conclusions

Though not easily comparable due to differences in methodology to reach diagnosis (i.e. psychiatric interviews and scales), population based studies generally indicate an increased risk of affective and anxiety disorders in patients with migraine, compared to non-migrainous subjects. There would also be a trend towards an association of migraine with bipolar disorder. By contrast, there is definitely no comorbidity with substance abuse/dependence. With respect to migraine subtypes, comorbidity (e.g. suicide attempts, bipolar disorder) mainly involves migraine with aura rather than the form without aura.

However, the lack of diagnostic recognition of certain forms of migraine, such as chronic migraine, due to the use of the first version of IHS criteria, may have significantly affected the results of several studies. Another limitation is that some of these studies were carried over within psychiatric research protocols, and thus were not originally designed to investigate the comorbidity between migraine and psychiatric disorders.

Apparently, no significant difference exists between migraine and tension-type headache patients in terms of prevalence of psychiatric comorbidity. By contrast, patients suffering from migraine show a decreased risk of developing affective and anxiety disorders compared to patients with chronic daily headache. It would also appear that affective and anxiety disorders prevail in patients with chronic forms of headache and substance use than in patients with migraine alone. Furthermore, patients with "transformed" (or chronic) migraine show an increased prevalence of affective and anxiety disorders compared to patients with simple migraine or chronic tension-type headache. Although early studies suggested that there is a correlation between frequency of headache and frequency of anxiety or depressive disorders, little evidence support a correlation between the severity of migraine and anxious or depressive symptoms.

In conclusion, the mechanisms underlying migraine psychiatric comorbidity are presently poorly understood, but issues concerning this topic remain a priority for future research. Psychiatric comorbidity indeed affects migraine evolution, may lead to chronic substance use and may change treatment strategies, eventually modifying the outcome of this important disorder.

Conflict of interest None.

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REVIEW ARTICLE

Overview of diagnosis and management of paediatric headache. Part II: therapeutic management

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Abstract A thorough evaluation of headache in children and adolescents is necessary to make the correct diagnosis and initiate treatment. In part 1 of this article (Özge et al. in J Headache Pain, 2010), we reviewed the diagnosis of headache in children and adolescents. In the present part, we will discuss therapeutic management of primary headaches. An appropriate management requires an individually tailored strategy giving due consideration to both non-pharmacological and pharmacological measures. Non-pharmacological treatments include relaxation training, biofeedback training, cognitive-behavioural therapy, different psychotherapeutic approaches or combinations of these treatments. The data supporting the effectiveness of these therapies are less clear-cut in children than in adults, but that is also true for the data supporting medical treatment. Management of migraine and TTH should include strategies relating to daily living activities, family relationships, school, friends and leisure time activities. In the pharmacological treatment age and gender of children, headache diagnosis, comorbidities and side effects of medication must be considered. The goal of symptomatic treatment should be a quick response with return to normal activity and without relapse. The drug should be taken as early as possible and in the appropriate dosage. Supplementary measures such as rest in a quiet, darkened room is recommended. Pharmaco-prophylaxis is only indicated if lifestyle modification and non-pharmacological prophylaxis alone are not effective. Although many prophylactic medications have been tried in paediatric migraine, there are only a few medications that have been studied in controlled trials. Multidisciplinary treatment is an effective strategy for children and adolescents with improvement of multiple outcome variants including frequency and severity of headache and school days missed because of headache. As a growing problem both children and families should be informed about medication overuse and the children's drug-taking should be checked.

Keywords Migraine · Tension-type headache · Symptomatic treatment · Pharmacological prophylaxis · Non-pharmacological treatment

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Introduction

Headache is the most common complaint in children and adolescents. The incidence of childhood migraine and frequent headache has substantially increased over the past 30 years. The increased incidence is alarming and may be secondary to lifestyle changes but also due to increased

awareness of the disease in this age group. Primary headache (especially migraine and tension type headache, TTH) is the most important cause of headaches in this age group. In part 1 of this article [1] we reviewed the diagnosis of headache in children and adolescents. In the present part, we will discuss therapeutic management.

Management of headaches

The general principles of management of headache in children and adolescents can be summarized as follows:

- Establish the diagnosis.
- Look for possible somatic and psychiatric comorbidities [2–6].
- Ask for triggers and assess degree of disability.
- Educate the child and family about the condition.
- Use a headache calendar to establish the characteristics of headache and associated symptoms.
- Establish realistic expectations and set appropriate goals.
- Discuss the expected benefits of pharmacological and non-pharmacological therapy and the time course to achieve them.
- Reduce the emotional mechanisms (on a personal level, within the family and at school) that provoke stress and may favour headache attacks.
- Advise to maintain a sound rhythm in daily life, which includes regular meals, sufficient fluid intake, physical exercise and sleep.
- Advise how to cope with trigger factors.

An algorithm for the diagnostic and therapeutic management of migraine is shown in Fig. 1.

Non-pharmacological treatments

Non-pharmacological treatment of migraine

Behavioural interventions, particularly biofeedback and relaxation therapy have demonstrated their effectiveness in the treatment of both adults and older children with migraine in controlled trials. The physiological basis for their effectiveness is unclear, but data from one trial suggest that levels of plasma beta-endorphin can be altered by relaxation and biofeedback therapies. The data supporting the effectiveness of behavioural therapies are less clear-cut in children than in adults, but that is also true for the data supporting medical treatment. This is due in part to methodological issues, especially the lack of specific tests for migraine, which has hampered research and helped leading to an inappropriate de-emphasis on care for childhood headache. In addition, migraine headaches in children are often briefer and have a higher rate of spontaneous remission than those experienced by adults, making it difficult to separate effective from ineffective treatments [7–9].

Starting from the consideration that children and adolescents with headache show greater indices of psychopathology [10–14] and show higher risk of developing psychological disorders in adulthood than healthy controls [15], different psychotherapeutic approaches are sometimes provided in clinical practice. Relaxation and cognitive-behavioural techniques have been found to reduce the intensity and frequency of headache in children and adolescents [16, 17].

Prospective, randomized, partly double-blind, placebo-controlled, parallel-group trial showed that Butterbur root extract and music therapy might be superior to placebo and may represent promising treatment approaches in the prophylaxis of paediatric migraine [18].

The specialists involved in the assessment and care of headache patients should strive to increase their knowledge of alternative therapies, so as to be better equipped to guide patients towards safe, economical and potentially effective treatments, rather than useless, costly or dangerous ones.

Non-pharmacological treatment of TTH

Behavioural headache treatments include relaxation training, biofeedback training, cognitive-behavioural therapy or combinations of these treatments. Among behavioural headache treatments, the two most common types of biofeedback for headache have been electromyographic biofeedback for TTH and "handwarming" or thermal biofeedback for migraine [9, 19–22]. Magnesium salt seems to be effective in treating the paediatric episodic and chronic TTH (ETTH, CTTH), but further well-controlled studies are needed [23].

There are restricted data about the natural history of childhood and adolescent TTH. It is accepted that over than 50% of the sufferers improve with a comprehensive headache managements. The most important predictors of prognosis are comorbid medical and psychological conditions and family problems [24, 25].

Pharmacological treatments

Pharmacological treatment of migraine

The data on efficacy and safety of medications in children are limited. Therefore, it may be necessary to use medications off label strictly weighing up the benefits and risks. However, medications which have shown efficacy in adults must not be used routinely in younger patients (please refer to Ref. [26]). Only few randomized placebo-controlled

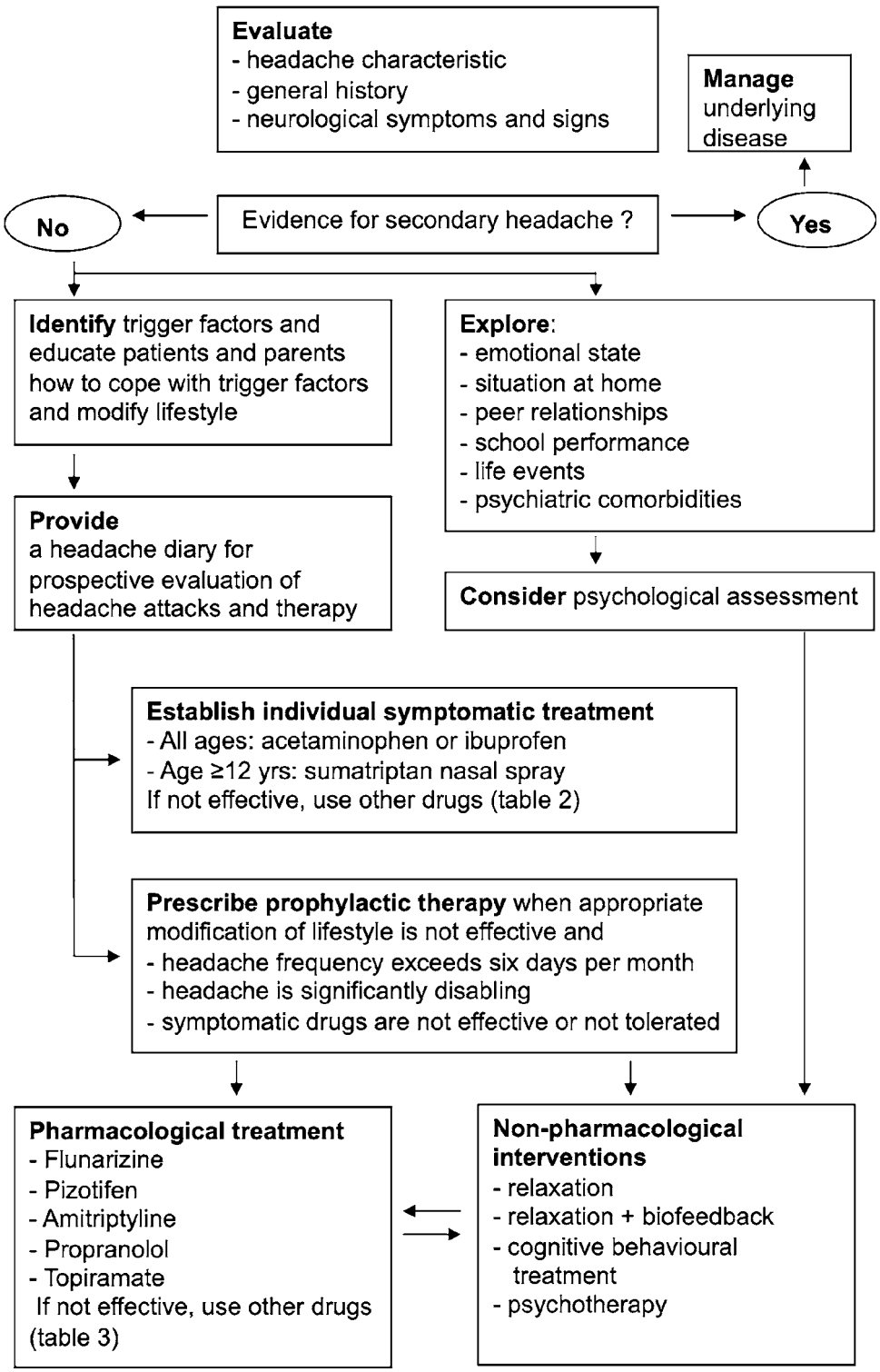

Fig. 1 Algorithm for the diagnostic and therapeutic management of migraine

clinical trials have been conducted in paediatric headache patients for both acute and preventive drugs. Moreover, the few published studies show a high placebo response rate in children, up to 55% for prophylactic drugs, up to 69% for symptomatic ones. Such high placebo response rates drastically reduce the possibility to find effective agents (in terms of statistically significant superiority over placebo) and may lower the interest of pharmaceutical companies and independent researchers to perform new clinical trials in this field. On the other hand, the placebo effect is a psychobiological phenomenon that can be attributed to different mechanisms [27]; it should be properly used by

the physician, simply bearing in mind that any medical treatment is surrounded by a psychosocial context that affects the therapeutic outcome.

The pharmacological treatment of migraine consists of symptomatic and/or prophylactic therapy. The former is aimed at relieving or ameliorating the symptoms of an acute attack, whereas prophylactic therapy, which requires the daily intake of medication for a certain period of time, decreases the frequency of the attacks and the severity of pain.

Symptomatic drug treatment The goal of treatment should be a quick response with return to normal activity and without relapse. Several key concepts should be made known to patients. Medication use should be limited to avoid medication overuse headache. It is important that an appropriate dose is used. Medications should be taken shortly after onset of migraine headache to optimize the effect, even though scientific evidence supporting this recommendation is lacking. The medication should be available to the patients also at school. Allodynia during a migraine in adults correlates with response to treatment of acute migraine with triptans and the progressive nature of migraine. This has emphasized the importance of early recognition of headache and appropriate treatment. Allodynia has recently been shown to be present in 37% of children during their migraine. Allodynia is often not routinely evaluated during a headache history even though there may be potential therapeutic implications. Prominent scalp symptoms include sensitivity to touch and difficulty brushing hair [28–30].

The available efficacy data about symptomatic drugs [31–46] are summarized in Tables 1 and 2. The following findings should be kept in mind:

- At 1 h acetaminophen tended to be slightly more effective (39% of children relieved) than ibuprofen (37% of children relieved), but 2 h after administration ibuprofen was more effective (68 vs. 54%).
- Sumatriptan nasal spray was superior to placebo and was well tolerated. No serious adverse events occurred with taste disturbance as the most common one.
- Pain relief at 2 h was achieved in significantly more attacks treated with rizatriptan 5-mg tablets (77%) or with rizatriptan 5-mg wafer (77%) than with standard care (64%).
- Pain relief rates after 2 h were 28% for placebo, 62% for zolmitriptan and 69% for ibuprofen (placebo vs. zolmitriptan $p < 0.05$; placebo vs. ibuprofen $p < 0.05$). Both drugs are well tolerated with only mild side effects.
- The Food Drug Administration has recently approved almotriptan for the acute treatment of migraine headache in adolescents. Nevertheless, almotriptan is still not approved in Europe.
- There are limited data about other triptans.
- In summary, there is moderate evidence that analgesics (acetaminophen and ibuprofen) and nasal-spray sumatriptan are more effective than placebo treatment. Based on the available literature, no differences in effect were found between the different compounds.

There is a lack of studies addressing the question of treatment in the emergency department of children with migraine. Future studies should focus on finding the best first-line agent for mild to moderate attacks in the emergency department and to confirm the usefulness of prochlorperazine as treatment for severe attack or status migrainosus. In the latter studies, attention should be given to adverse drug reactions associated with prochlorperazine. Furthermore, treatment to decrease the recurrence of migraine attack and the need for rescue medications after discharge from the emergency department should also be carefully evaluated [30, 48].

Prophylactic drug treatment Pharmaco-prophylaxis is only indicated if lifestyle modification and non-pharmacological prophylaxis alone are not effective. Although many prophylactic medications have been tried in paediatric migraine, there are only a few medications that have been studied in controlled trials. Prophylactic medications are recommended only when migraines are occurring with sufficient frequency (usually 3–4 per month) and severity to impact a patient's daily function or quality of life (e.g. missing school). To minimize adverse effects, prophylactic medications are started at the lowest dose and titrated upward as needed. They have to give a through time period (at least 4–6 months), and both comorbidities and side effects of the drug have to be taken into consideration [30, 49].

Prophylactic drugs evaluated in placebo-controlled and open-label trials for migraine [50–71] have been summarized in Table 3. The following findings should be kept in mind:

- Flunarizine is an effective drug. Its use is limited by daytime sedation found in 10% of the patients and weight gain in more than 20%. Because of probable D2 receptor interaction it should not be given for more than 3 months (administering it in the early evening can avert daytime sleepiness, dosage 5 mg/die) [72, 73].
- Propranolol was found to be superior to placebo in one randomized controlled trial and not effective in two others. It was found to activate asthma in subjects with atopic disorders or a positive history of atopic disorders, and there are no follow-up studies concerning long-term risks of betablockers. Therefore, some centres do not use betablockers for migraine prophylaxis in children.
- The overall positive response rate of cyproheptadine was 83% and common side effects included sedation and increased appetite.

Table 1 Symptomatic drugs for migraine management evaluated in placebo-controlled and open clinical trials

References	Drug	Study design	Evidence level	Dose	Age (years)	Number of patients	Responders (%)		*p* value
							Active drug	Placebo	
Hamalainen et al. [31]	Ibuprofen	RCT	A	10 mg/kg	4–16	88	68	37	<0.05
Lewis et al. [32]	Ibuprofen	RCT		7.5 mg/kg	6–12	84	76	53	0.006
Evers et al. [33]	Ibuprofen	RCT		200–400 mg	6–18	32	69	28	<0.05
Hamalainen [31]	Acetaminophen	RCT	B	15 mg/kg	4–16	88	54	37	<0.05
Hamalainen et al. [34]	Dihydroergotamine	RCT	C	20, 40 μg/kg	5–15	12	58	16	NS
Ueberall [35]	Sumatriptan nasal	RCT	A	20 mg	6–10	14	86	43	0.03
Winner et al. [36]	Sumatriptan nasal	RCT		5–10–20 mg	12–17	510	66[a]	53	<0.05
Ahonen et al. [37]	Sumatriptan nasal	RCT		10–20 mg	8–17	83	64	39	0.003
Winner et al. [38]	Sumatriptan nasal	RCT		20 mg	12–17	738	61	52	NS
Hamalainen et al. [39]	Sumatriptan oral	RCT	C	50–100 mg	8–16	23	30	22	NS
Mac Donald [40]	Sumatriptan sc.	OT	C	3–6 mg	6–16	17	64	–	–
Linder [41]	Sumatriptan sc.	OT		0.06 mg/kg	6–18	50	78	–	–
Winner et al. [42]	Rizatriptan	RCT	C	5 mg	12–17	196	66	56	NS
Visser et al. [43]	Rizatriptan	RCT		5 mg	12–17	234	68	69	NS
Visser et al. [43]	Rizatriptan	OT		5 mg	12–17	686	77	–	–
Linder and Dowson [44]	Zolmitriptan oral	OT	C	2.5–5 mg	12–17	38	88–70	–	–
Evers et al. [33]	Zolmitriptan oral	RCT		2.5 mg	6–18	32	62	28	<0.05
Charles [45]	Almotriptan oral	OT	B	6.25–12.5 mg	11–17	15	86	–	–
Linder et al. [46]	Almotriptan oral	RCT		6.25–12.5–25 mg	12–17	866	67–73	55	<0.001

Evidence level: findings regarding symptomatic drugs were reviewed and the recommendations were categorized into different levels (A–C) [47]. Level A: two or more clinically controlled, randomized studies carried out according to good clinical practice (GCP), versus placebo or versus active treatment of proven efficacy. Level B: one clinically controlled, randomized study carried out according to GCP or more than one well-designed clinical case–control study or cohort study. Level C: favourable judgment of two-third of the Ad Hoc Committee members, historical controls, non-randomized studies, case reports

NS no statistically significant difference between active drug and placebo, *RCT* randomized controlled trial, *OT* open trial

[a] 5 mg

Table 2 Summary of the efficacy of medication used to treat acute migraine attacks in children and adolescents [45]

	Outcome			
	Pain relief	Pain-free	Recurrence	Need for rescue medications
Oral medication				
Acetaminophen ($n = 1$)	+	−	−	−
DHE ($n = 1$)	−	−	−	−
Ibuprofen ($n = 3$)	+	±	−	±
Rizatriptan ($n = 3$)	±	−	−	±
Sumatriptan ($n = 1$)	−	±	−	−
Zolmitriptan ($n = 2$)	±	±	−	+
Intranasal medication				
Sumatriptan ($n = 4$)	±	±	−	±
Intravenous medications				
Prochlorperazine ($n = 1$)	+	?	−	?
Ketorolac ($n = 1$)*	?	?	?	? ±

+ studies showing consistent positive results or a study showing positive result; − studies showing consistent negative results or a study showing negative result; ± studies showing inconsistent results; ? not evaluated

* Used as a comparative agent against prochlorperazine

Table 3 Prophylactic drugs for migraine management evaluated in placebo-controlled and open clinical trials

References	Drug	Daily dose	Age in (years)	Number of patients	Study design	Evidence level	% responders or p values (*)
Antihypertensive drugs							
Ludvigsson [50]	Propranolol	60–120 mg	7–16	28	RCT	C	82 vs. 14%
Forsythe et al. [51]	Propranolol	80 mg	9–15	39	RCT		NS
Olness et al. [52]	Propranolol	3 mg/kg	6–12	28	RCT		NS
Sillampää [53]	Clonidine	25–50 μg	≤15	57	RCT	C	NS
Sills et al. [54]	Clonidine	0.07–0.1 mg	7–14	43	RCT		NS
Calcium channel blockers							
Guidetti et al. [55]	Flunarizine	5 mg	10–13	12	OT	A	66%
Sorge et al. [56]	Flunarizine	5 mg	5–11	63	RCT		$p < 0.001$ (HA frequency) $p < 0.01$ (HA duration)
Visudtibhan et al. [57]	Flunarizine	5–10 mg	7–15	21	OT		%66
Battistella et al. [58]	Nimodipine	10–20 mg	7–18	37	RCT	C	NS
Serotonergic drugs							
Gillies et al. [59]	Pizotifen	1–1.5 mg	7–14	47	RCT	C	NS
Lewis et al. [60]	Cyproheptadine	2–8 mg	3–12	30	OT	C	83%
Antidepressants							
Battistella et al. [61]	Trazodone	1 mg/kg	7–18	35	RCT	C	NS
Hershey et al. [62]	Amitriptyline	1 mg/kg	9–15	192	OT	C	80%
Lewis et al. [60]	Amitriptyline	10 mg	3–12	73	OT		89%
Anticonvulsants							
Caruso et al. [63]	Divalproex sodium	15–45 mg/kg	7–16	42	OT	B	76%
Sedaroglu et al. [64]	Divalproex sodium	500–1,000 mg	9–17	10	OT		$p = 0.000$ (HA severity) $p = 0.002$ (HA frequency) $p = 0.001$ (HAduration)
Hershey et al. [65]	Topiramate	1.4 ± 0.7 mg/kg	8–15	75	OT	A	$p < 0.001$ (HA frequency)
Winner et al. [66]	Topiramate	2–3 mg/kg	6–15	162	RCT		NS
Lewis et al. [67]	Topiramate	100 mg	12–17	103	RCT		72%
Miller [68]	Levetiracetam	250–1,500 mg	3–17	19	OT	B	$p < 0.0001$ (HA frequency)
Pekalnis et al. [69]	Levetiracetam	250–1,500 mg	6–17	20	OT		$p < 0.0001$ (HA frequency)
Belman et al. [70]	Gabapentin	15 mg/kg	6–17	18	OT	C	80%
Pakalnis and Kring [71]	Zonisamide	5.8 mg/kg	10–17	12	OT	C	66%

Evidence level: findings regarding symptomatic drugs were reviewed and the recommendations were categorized into different levels (A–C) [47]. Level A: two or more clinically controlled, randomized studies carried out according to good clinical practice (GCP), versus placebo or versus active treatment of proven efficacy. Level B: one clinically controlled, randomized study carried out according to GCP or more than one well-designed clinical case–control study or cohort study. Level C: favourable judgment of two-thirds of the Ad Hoc Committee members, historical controls, non-randomized studies, case reports

NS no statistically significant difference between active drug and placebo, *HA* headache, *RCT* randomized controlled trial, *OT* open trial

* The % is expressed as overall % of responders (OT) or active-drug vs placebo % of responders (RCT); p values refer to active drug versus placebo comparisons (RCT) or pre-treatment versus post-treatment comparison of headache characteristics (OT)

- There are limited confirmative data about trazodone.
- Amitriptyline (1 mg/kg) is an effective drug with an 84.2–89% positive response rate and only mild sedation was reported as side effect.
- Divalproex sodium (15–45 mg/kg/day) is an effective drug with 50% headache reduction seen in 78.5% of patients, 75% reduction in 14.2% of patients, and 9.5% of patients became headache-free after 4 months of treatment. The observed side effects were dizziness, drowsiness and increase in appetite.
- Topiramate is an effective drug for the reduction of headache frequency, severity and duration. The most common side effects reported were cognitive (12.5%), weight loss (5.6%) and sensory (2.8%).
- There are limited data about levetiracetam, gabapentin and zonisamide.

Pharmacological treatment of TTH

Most TTH is best managed by primary care. ETTH is self-limiting, but children and their parents generally consult doctors when headaches occur frequently and are no longer responsive to analgesics. Medication overuse can be a common problem in patients with frequent headache. The treatment of migraine and TTH overlaps. Both require acute treatment, either behavioural or pharmaceutical. Behavioural treatment is needed for all types of TTH. Preventive pharmaceutical treatment is needed for frequent TTH if lifestyle modification and non-pharmacological treatment alone are not effective. Although childhood TTH is often treated with medication, few studies have been published the efficacy of medication in paediatric TTH. More studies in children need to be done regarding the treatment of this common disorder. The lack of availability and cost of non-pharmacological interventions might diminish the use of some treatment modalities [74, 75].

For acute treatment of ETTH, paracetamol, aspirin and combination analgesics are effective and inexpensive drugs. Non-steroidal anti-inflammatory drugs are also effective first-line therapeutics for ETTH in adults. In children younger than 15 years, aspirin is not recommended because of the concern regarding Reye's syndrome. Paracetamol seems to be safe even in young children [75–78].

Frequent headaches in children and adolescents often require preventive management. Prophylactic pharmacological treatment should be considered in CTTH if non-pharmacological management is inadequate. For children with frequent headache, amitriptyline might be beneficial, although no placebo-controlled studies have been performed [62].

Treatment of cluster headache

Several treatment alternatives have been tried in cases reported in the literature. According to these data, the most effective symptomatic treatments are oxygen [79–82], sumatriptan [81, 83] and acetylsalicylic acid [80–84]. Prophylactic treatments reported in literature are prednisone/prednisolone [85, 86], indomethacin [84], pizotifen [81], verapamil [81, 82, 87], methysergide [79, 83, 85], loratadine [88], astemizole [88] and flunarizine [89]. No controlled study has been reported.

If oxygen is administered at the onset of an attack via a non-rebreathing facial mask at a flow rate of at least 7 l/min, approximately 70% of patients will obtain pain relief within 15 min. This therapy has obvious practical limitations and requires oxygen being readily available at the patient's home [85, 90]. Considering the unbearable pain intensity, off-label use of sumatriptan nasal spray or subcutaneous sumatriptan may be necessary. Ergotamine has also been used. It is not recommended for acute CH-treatment in children, but might be given in the evening for preventing night-time attacks. Children between 6 and 9 years of age should receive 0.1 mg/dose, those between 9 and 12 years of age should receive 0.5 mg, and those between 12 and 16 years of age should receive 0.75 mg/dose. Lidocaine applied with a spray bottle or by dropping in the nostril ipsilateral to pain achieves moderate pain relief, and it may be useful as an adjunctive therapy. Although the reason for steroid efficacy is unknown, the use of cortisone in the acute period can stop the attacks and may help to prevent further attacks. In adolescents a marked relief of cluster headache in 77% of 77 episodic cluster headache patients, and a partial relief in another 12% of patients treated with prednisone was reported [85, 90]. For prophylactic treatment the efficacy of verapamil has been attributed to a possible stabilization of vascular tone. It is generally well tolerated and can be used in combination with corticosteroids, sumatriptan and ergotamine [91, 92].

Life quality of headaches

Health-related quality of life (QOL) is an emerging area of headache research with a direct impact on patient adherence, patient satisfaction and treatment effectiveness. On the other hand, the assessment of QOL in children is difficult, since measures must consider children's changing cognitive and social development [93, 94]. Data-based analyses revealed that children with frequent or severe headaches (FSH) were significantly more likely than those without FSH to exhibit high levels of emotional, conduct, inattention-hyperactivity, and peer problems and were significantly more likely than children without FSH to be upset or distressed by their difficulties and to have their difficulties interfere with home life, friendships, classroom learning and leisure activities [95]. Subjects familiar with headache experienced more stress, fatigue, depression, and somatic symptoms; they felt less strong, had a less cheerful mood and reported lower satisfaction with health and with life in general than the subjects who never had headaches [96]. The impact of headaches on QOL is similar to that found for other chronic illness conditions, with impairments in school and emotional functioning being the most prominent [97]. Headache is the third most common cause among illness-related causes of school absenteeism resulting in substantial impairment among paediatric patients [98]. A specific questionnaire (PedMIDAS) provides a tool to assess the impact of migraines in children and to monitor response to treatment. Further research should focus on additional validation of the PedMIDAS

using a larger population and sampling from other populations (e.g. primary care and community samples) [99].

Conclusions

- Management of migraine and TTH should include strategies relating to daily living activities, family relationships, school, friends and leisure time activities.
- Management should be completed by education (both of the children and parents), non-pharmacological interventions and psychosocial support.
- With reference to symptomatic treatment, the drug should be taken as early as possible and in the appropriate dosage. In cases with early onset of nausea and/or vomiting endorectal or parenteral administration should be preferred. Antiemetic drugs should not be provided if the child vomits only once or headache stops after vomiting. If an antiemetic is required, ondansetron may be preferred for its good tolerability. Supplementary measures such as rest in a quiet, darkened room is recommended.
- Multidisciplinary treatment is an effective strategy for children and adolescents with improvement of multiple outcome variants including frequency and severity of headache and school days missed because of headache.
- In the pharmacological treatment age and gender of children, headache diagnosis, comorbidities, need and side effects of medication must be considered.
- As a growing problem both children and families should be informed about medication overuse and the children's drug-taking should be checked.
- Regular follow-up care is needed, especially for those children with more severe initial headache presentation.

Conflict of interest None.

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Cervicogenic Headache: A Real Headache

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Abstract Although theories regarding headache originating in the neck have existed for more than 150 years, the term "cervicogenic headache" originated in 1983. Early descriptions pinpoint the characteristic symptoms as dizziness, visual disturbances, tinnitus, and "posterior" headache, conceivably as a consequence of arthrosis, infliction upon the vertebral artery, or with a "migrainous" background and occurring in "advanced age." Cervicogenic headache (mean age of onset, 33 years) displays a somewhat different picture: unilateral headache, starting posteriorly, but advancing to the frontal area, most frequently the main site of pain; usually accompanied by ipsilateral arm discomfort, reduced range of motion in the neck, and mechanical precipitation of exacerbations (eg, through external pressure upon hypersensitive, occipital tendon insertions). Treatment options in treatment-resistant cases include cervical stabilization operations and extracranial electrical stimulation. In a personal, population-based study of 1,838 individuals (88.6% of the population), a prevalence of 2.2% "core" cases was found.

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Introduction

In the beginning, there was only migraine. This was the situation for many centuries. Then, sporadic reports about a more or less correctly described cluster headache started to appear on the firmament. But, it was not until just before the last world war that Horton et al. [1] described such a headache in so correct terms and in such a number that it soon became part of the general neurologist's and, with time, the general practitioner's life [2].

"Tension headache" originated somewhere along the road; it is somewhat uncertain exactly when. In 1954, Tunis and Wolff [3] stated that "It has been *established* that some headaches arise from sustained contraction of skeletal muscle about the face, scalp, and neck."

Thus, these were the "established" large/relatively large, and probably primary headache groups in the early 1970s. Roughly stated, there was at the time in the Anglo-Saxon, as opposed to German/French medical literature, close to zero mention of any particular headache, conceivably stemming from the neck, neither in textbooks nor at headache meetings. Not even in the then-accepted headache classification system [4] was there any mention of it, other than the general allusion to the possibility of "Headaches due to spread of pain from noxious stimulation of other structures of the cranium and *neck* (periosteum, joints, ligaments, muscles, or cervical roots)." No description of the clinical picture of such a headache was given. Heyck [5], one of the most able headache clinicians ever, complained that the possibility that headache might stem

from the neck was stepmotherly treated in the classification, since this possibility was only mentioned "en passant."

This does not imply that serious attempts at defining such a headache had not been made previously. At first, there must have been a prolonged period of more or less pure speculation. Nerves, originating in the cervical spine, furnish the nerves to the posterior scalp; why could pain not originate in this network? Any convincing exactitude in these speculations could not be expected, but more or less by chance, there may have been some correct, clinical elements about these early attempts. Another phase started with Barré's "syndrome sympathique cervical posterieur" [6]. The predominantly occipital headache was combined with dizziness, which was magnified to become an essential feature. This work caused no breakthrough. Further steps were taken by Baertschi-Rochaix [7], who described "migraine cervicale," in other words a *migraine* variant. The cardinal symptoms were enumerated as such: predominantly occipital headache, dizziness, "ear noise," and visual disturbances, in conformity with Barré's description. It was considered a traumatic syndrome, and a characteristic roentgenologic finding was obligatory (ie, uncovertebral deformation). Reduction in neck movement and increased tenderness of nuchal structures were occasionally present. However, little emphasis was put on these last observations. Migraine, a *primary* headache, was described. However, "cervicale" alludes to a putative, structural phenomenon, in other words to a *secondary* headache, with an allusion to a *contradictio in adjecto*. The *term* itself may have rendered a lethal blow to this description. Neurologists around the world probably were confounded: the concept itself (ie, that *migraine* could originate in the neck) might have seemed incomprehensible at the time. The connection with present-day cervicogenic headache (CEH) remains doubtful—"migraine cervicale" being a disorder of the "advanced age." That a genuine CEH had been described seems highly unlikely.

In the late 1970s and early 1980s, in the western world, one would draw extremely negative commentaries if one voiced opinions to the effect that *headache* might originate in the cervical area. Nevertheless, we ventured to present this idea during the first World Congress of Headache in 1983 [8] and could witness the profound disbelief at close range toward this concept and toward the term "cervicogenic headache," coined at the time. The hefty, stubborn, and protracted opposition is the best proof that the concept of CEH was far from being accepted at the time. A series of 22 patients, seemingly fitting into this category, was presented [8]. Grossly, the criteria used at the time still seem acceptable. This latter move may represent another thrust to gain acceptance for CEH as a separate headache.

Clinical Picture

In its clinically recognizable form, CEH is characterized by unilaterality/unilateral preponderance of head pain, the unilaterality being without side alternation. The unilaterality is particular, in that frequently/regularly a co-involvement of the opposite side takes place, notably when the headache is strong. However, also on such occasions, the symptomatic side headache is the stronger one. Unfortunately, investigators frequently mix up this situation with a proper bilaterality.

Furthermore, CEH is characterized by the following: reduced range of motion (ROM) in the neck; mechanical precipitability of attacks/exacerbations, either by prolonged, awkward neck positioning or by external pressure against circumscribed, hypersensitive areas (eg, tendon insertions), ipsilaterally in the occipital area (the awkward neck position "method" being the more reliable of the two methods, for generating heavy attacks); and ipsilateral neck pain that frequently spreads to shoulder/arm, either with a radicular pattern or more diffusely. Pain exacerbations generally start in the neck/occipital area (Vågå study: 97% of the cases [9•]) and then spread to the forehead, and at the maximum, forehead pain may be as marked as, or even stronger than, posterior pain. Pain may transitorily be clearly reduced or even almost abolished by anesthetic blockades of occipital or cervical nerves. It should be stressed that blockades have not been carried out in several recent studies (eg., the Vågå study [9•]). The reasons for this may vary: 1) lack of setup for blockades; 2) too low pain level, on the given occasion, for blockades to render meaningful results; or 3) uncertainty as to where to deposit the anesthetic agent. Although blockades presently are an obligatory part of diagnostics in scientific work [10], it may seem somewhat rigid to demand routine blockades at this stage. With increased understanding of this disorder (where to anaesthetize), there may again be a place for obligatory blockades.

The CEH diagnostic criteria [10] are 1) unilaterality of pain; 2) reduction, range of neck movement; 3) ipsilateral shoulder discomfort; and 4) ipsilateral arm discomfort; mechanical precipitation of exacerbations/attacks by 5) awkward neck positions or 6) external pressure against sensitive occipital structures. (In this presentation, "shoulder" and "arm" are given one number each). Blockades have already been mentioned.

In the Vågå study [9•], headache onset posteriorly, with eventual spreading to the forehead was a free variable, but proved to be almost invariably present (Table 1) and for that reason should probably be included among the regular CEH criteria. Presently, CEH seems to be the only headache that regularly is unilateral, starts posteriorly, and then moves to the front.

Table 1 Characteristic clinical traits in pertinent headaches

Clinical trait	CEH	T-TH	M-A
Unilaterality,%	100	8	52
Mechanical precipitation,%	100	4	4
Posterior onset, attacks,% [a]	97	30	22
Throbbing pain quality,%	20	22	81
Chronicity of pain[b]	+	−/+	−
Diffuse arm discomfort,%	100	7	8
Restriction, ROM,%[c]	93	17	16
Photophobia,%	19	15	68
Cervicogenic factor	2.37	0.72	0.93

[a] CEH versus M-A: $P<0.001$ (chi-squared test)

[b] *Plus sign* (+) indicates invariably/close to invariably present; *Minus/plus sign* (−/+) indicates may or may not be present; *Minus sign* (−) indicates generally not present

[c] Reduction of rotation: ≥15°

CEH—cervicogenic headache; M-A—migraine without aura; T-TH—tension-type headache

(*Data from* Sjaastad and Bakketeig [9].)

A simple enumeration of the mentioned criteria is most useful in foretelling a diagnosis of CEH. The Vågå study [9•] showed a close-to-complete congruity between the orthodox application of the criteria and the enumeration.

There is one good-sized, population-based study of headache epidemiology with personal examination of all the participants: the Vågå study [9•]. Results from this study are used herein. An ultra-brief outline, therefore, seems appropriate. Headache was studied in 1838 (88.6%) of the 18- to 65-year-old citizens in the rural commune of Vågå, southern Norway, in the course of a 2-year period. A "core" version of CEH was observed in 2.2% of the study group. CEH cases mixed with tension-type headache (T-TH) and migraine have not been and probably should not be used in such calculations [9•].

In the Vågå study [9•], there seemed to be a certain male preponderance (female/male: 0.71). In a hospital-based series, however, a female preponderance (eg, 2.0 [8]–5.4 [11]; even: 7.2) has been observed [12]. This marked variation has its explanation—a relatively mild CEH form, not leading to consultations, seems to prevail in the population at large. Those consulting physicians are mainly female. In the Vågå study, males, generally, and to a high degree those with CEH, tended to come for an appointment in the final phase. If the study had been interrupted at an earlier stage than at 88.6%, there would have been a female preponderance also in the Vågå study.

To assess the given prevalences, the following should be appreciated: CEH diagnosis is no left-hand work. Mechanical precipitation of attacks and neck mobility examinations are sine qua non for the CEH diagnosis. The consequences of the three last dictums are serious: CEH diagnosis can never be based on questionnaires, with for example no possibility for mechanical precipitation tests. CEH diagnostic work can never be left to assistants/apprentices, in any part of the selection process. Investigators who on the one hand demand blockades, but on the other accept prevalence studies based on questionnaires, have an insurmountable dilemma. Hospital-based studies can only show the relative prevalence versus other headaches (ie, in the hospital clientele); they do not reflect the grass-root situation. The same goes for the sex ratio.

CEH as such can start as early as in the late teens; in the Vågå study [9•], the mean age of onset was around 33 years. CEH usually starts out as a weak, episodic headache, the solitary aggravations being precipitated; with time, a chronic fluctuating course develops (invariably?). This gradual development of the symptoms is typical for CEH. A more abrupt onset may create suspicion of a traumatic genesis or a symptomatic case [13••].

The head pain itself is generally moderately intense (ie, a mean value of 3.8+, on a 0–6+ scale [9•], compared with 4.2+ for migraine without aura, and 3.1+ for T-TH) (Table 1). A relatively fixed frame regarding attack duration is typical of unilateral headaches, such as trigeminal neuralgia, SUNCT (Short-lasting, Unilateral, Neuralgiform headache attacks with Conjunctival injection and Tearing) syndrome [14], and chronic paroxysmal hemicrania (CPH) [15]. A characteristic CEH trait is lack of regularity in this respect. In the solitary patient, exacerbations usually last from a couple of hours to weeks. Reduction in the ROM in the neck is also a relatively important observation diagnostically. To be positive, rotation should probably be reduced by ≥10°. In the Vågå study [9•], a rotation reduction of ≥15° was present in 93% of the cases.

Mechanical Precipitation of Attacks

A fundamental characteristic of CEH is that what may appear to be exacerbations similar to spontaneous ones can be precipitated mechanically. This distinguishes it from otherwise rather similar headache forms. In trigeminal neuralgia, paroxysms can be precipitated *frontally.* In two headaches (ie, in CPH with a mechanical precipitation component [16] and in CEH), headache can be precipitated from *posterior* sites. In spite of this similarity, CPH is easily distinguished from CEH by the following: its absolute response to moderate indomethacin dosages, its relatively short duration, its excessively severe attacks, and its marked autonomic signs (eg, ipsilateral lacrimation and conjunctival injection) [15].

Because of their importance, we will take a closer look at the precipitation mechanisms. The external digital pressure is exerted with the thumb, at a 90-degree angle

with the skin. One can train oneself, by using scales, to exert a pressure of 3 to 4 kg [17]. For the investigator, reiterated checking is imperative to preserve this quality. For practical purposes, this simple method suffices. Of course, one can also use algometers. In fibromyalgia (FM), such pressure (ie, 4 kg) is used to sort out "tender points" [18].

It is a common misunderstanding that one can provoke head pain in healthy individuals to the same extent as in some headache categories by exerting external pressure (eg, over identified tendon insertions in the occipital area). In healthy individuals, such pressure, even when doubled, will only lead to a mild, transitory, local discomfort, occasionally spreading to the occipital area. In CEH, a pressure of 3 to 4 kg over sensitive spots will generally lead to both local and spreading pain, outlasting the stimulus by more than just a few seconds. Occasionally, discomfort/pain spread to the forehead. A doubling of the pressure (6–8 kg) frequently produces an exacerbation/attack in particular patients/particular situations [17].

Digital pressure (ie, 3–4 kg) directly applied against certain neck structures seems to discriminate fairly well between patients and healthy individuals [9•, 17]. A clearly positive test on the symptomatic side is a relatively strong signal for CEH. In the absence of a positive test, at this stage of development, it is hard to establish a CEH diagnosis. Whether attacks at all can start spontaneously is hard to ascertain.

The one who is searching for something that he does not know exactly what it is may be in big trouble. During our wholehearted search for CEH cases in the middle/late l970s, we were darting hither and thither for a long time. In a putative CEH, would there be unilateral/bilateral head pain; occipital/whole head pain; chronic/recurring pain; moderate/high intensity pain; old age/any age onset; clear/discrete neck symptoms and signs? Would there be characteristic "migrainous" symptoms, such as nausea and photophobia? Undoubtedly, one major guideline in the search for the first CEH case was the aforementioned fact that it had already been established that in the occasional CPH patient, attacks could be precipitated mechanically in two different ways: 1) pressure against hypersensitive spots in the cervical area, and 2) protracted, awkward head positioning. Examination of hypersensitive cervical/nuchal sites could be carried out in various ways: 1) a threshold for painful response is sought, or 2) as in our work, a set stimulus strength is used to find the number of positive responses.

In CPH (the prototype), a meticulous, repetitive search was made centimeter for centimeter in the occipital area and around the whole circumference of the neck, and several hypersensitive areas were detected, among them the groove behind the mastoid process; and, maybe above all, the anterior aspects of the transverse processes of C4/C5. Solitary attacks could regularly be elicited from these areas in a period of frequent and severe attacks (Table 2).

A breakthrough regarding CEH came at the end of the 1970s [8]: A 30+-year-old female could regularly generate head pain by rotating the neck (eg, when backing the car). The headache was unilateral without a side shift, moderately intense, and symptom poor; it could be precipitated mechanically, and its duration by far exceeded the duration of the stimulus. This clinical picture seemed to differ clearly from that of migraine, tension headache (the later "T-TH"), and cluster headache. The search for areas from where attacks could be provoked started in this patient and similar patients, who came to our cognizance, using CPH as a prototype.

Grossly, there was a striking similarity between hypersensitive areas in CPH and CEH (Table 2). Nevertheless, there was a real difference, as the C4/C5 transverse processes were more sensitive in CPH than in CEH. In CPH, it was originally felt that the area around the carotid artery was sensitive; some type of carotidynia was

Table 2 Hypersensitive areas of CPH and CEH

Location	CPH	CEH
Groove behind mastoid process	++	++
GON/MON	+	+
Transverse processes, C4/C5	++	((+))
Tendon insertions, along bony ridge: protuberantia occipitalis externa, mastoid process	+	++
Upper part sternocleidomastoid muscle[a]	?	++

This version represents the current practice, after some mostly minor adjustments from the original version

One plus sign and *two plus signs* represent two clearly different degrees of responses; with (+) there may or may not be a weak response

[a] The hypersensitive area may correspond to the area where the MON crosses over the dorsal margin of the muscle

CEH—cervicogenic headache; CPH—chronic paroxysmal hemicrania; GON—greater occipital nerve; MON—minor occipital nerve

(*Data from* Sjaastad [2] and Sjaastad et al. [16].)

suspected. Later, the focus of interest proved mostly to be localized lateral to the artery and, ultimately, along the transverse processes. There are various reasons why C4/C5 have fallen out of use in CEH: first, C4/C5 pressure seemed less effective in producing attacks in CEH than the posterior sites; next, for routine use, they are less easily identifiable, anatomically, than the posterior sites.

There are other differences between the mechanical pressure responses in the two disorders: The response generally appears within seconds in CPH, whereas in CEH it takes minutes or more; in CEH, the response may even be two-phased: first an early response and then, after hours, exacerbation/attack.

Differential Diagnosis

CEH was originally sorted out from the categories of migraine and T-TH. Therefore, these two headaches are still major diagnostic alternatives. In CEH, attacks generally last longer than in migraine (Table 1). Head pain in CEH does not shift side. Furthermore, CEH attacks to a much lesser degree than migraine attacks are accompanied by typical "migrainous" symptoms. Symptoms and signs pertaining to the neck are important indicators of CEH. CEH attacks/exacerbations typically start in the neck, whereas migraine attacks more frequently than not seem to start anteriorly (Table 1). Pure forms of T-TH and CEH are usually easily separable [12]. Even with CEH in its bilateral form, there are actually many features left on which to base a differential diagnosis (Table 1).

There are also the features indicative of cervical abnormality (cervicogenic factor [CF]), a summation factor, consisting of five solitary elements [17]: 1) ROM deficit; 2) skin-roll test, shoulder area; precipitation of head pain with 3 to 4 kg of external pressure against: 3) occipital area tendon insertions; 4) musculus splenius/upper musculus trapezius area; and 5) cervical facet joint tenderness. The mean CF value in headache-free inhabitants in the Vågå study [9•] was 0.42 (mean total Vågå study: 0.79; T-TH: 0.72; migraine without aura: 0.93, compared with CEH: 2.37).

Fibromyalgia and Myofascial Pain

It has been claimed, mostly via hearsay, that fibromyalgia (FM) might be hard to distinguish from CEH. FM seems to be characterized by tender points and widespread, *bilateral* pain, both below and above the waist. A rather vague headache is an integral part of FM in more than 50% of the cases. Tender points, by definition a sine qua non in FM, should be present in at least 11 of 18 defined points [18, 19]. By contrast, CEH is a *localized* disorder and *unilateral* at that. Hypersensitive site stimulation in CEH causes a spreading pain, whereas FM tender point stimulation does not. Restricted ROM is a frequent finding in CEH. The two disorders seem incompatible.

CEH and myofascial pain (MFP) both are regional pain syndromes [18–20]. Unilaterality has not been emphasized in MFP, but is a characteristic trait of CEH. The MFP trigger spots are found in muscles, whereas CEH hypersensitive sites are over tendons, bones, or nerves. Prognosis in MFP seems favorable, whereas CEH has a tendency toward chronicity. The treatment modalities in the two disorders differ entirely, with cervical stabilization operations pertaining only to CEH. MFP does not fulfill the criteria of CEH [10], and vice versa.

It has nevertheless been claimed that the original CEH concept has been thwarted, CEH being best understood as a MFP syndrome plus some cervical derangement [21]. In one study, five alleged CEH patients had been treated as though they were MFP patients [21]. Unfortunately, the CEH diagnosis at face value seemed acceptable in only two of the patients, in whom all the four criteria, applied in this study, were fulfilled. One patient lacked one criterion; one lacked two, and one lacked three out of the four criteria used. CEH diagnosis is in general difficult. Moreover, the actual study was carried out in a setting with little or no tradition for CEH diagnostics. A number of trigger points ($n=14$) were examined, with half of them being situated outside the traditional, hypersensitive areas in CEH. Following long-term, traditional MFP therapy, a durable improvement of pain and trigger point sensitivity was obtained. This does not have much relevance for CEH as such. In a study of CEH, the diagnostic criteria for CEH must be adhered to, and not those of MFP.

All in all, we feel that MFP is an overinflated term and that trigger points have been invoked to explain an expanding number of disorders. The development around MFP is reminiscent of what ultimately happened around hyperostosis frontalis interna (HFI) (Morgagni-Morel syndrome [22]): When an anomaly (HFI) is observed in a great number of disorders, then it is probably of little or no consequence in any of them.

Comments

CEH seems to be a headache in its own right. Mechanical precipitation of attacks, decreased ROM in the neck, and ipsilateral shoulder/arm complaints actually afford compelling evidence that this headache stems from the neck. The headache arising in tractor drivers is another argument; headache (and/or neck ache) was present in 84% of them during chores, and there was no headache without a neck ache.

With intracranial space occupying disorders, head pain and upper extremity symptoms would tend to be on

different sides [23, 24]. The fact that in CEH head and arm pain/discomfort are on the same side attests to a nuchal/cervical origin of the complaints, with the pathology on the pain side.

Kerr and Olafsson [25] demonstrated convergence of cervical and trigeminal dorsal root afferents in the upper cervical cord. This may explain the "illusion" that pain originating in the neck appears as though it comes from the front.

CEH is a secondary headache and a syndrome. CEH may seem to be a final common pathway. However, the mechanisms underlying the pain need to be sorted out. The facts below may give some direction for this search:

1. CEH is not a disorder of the degenerative age, the mean age of onset being 33 years.
2. The pain seems to be neuropathic and not nociceptive, because morphine does not work properly [26], whereas dorsal column electrical stimulation seems to work.
3. In CEH with upper extremity radicular pain, removable disc protrusions seem to play a causative role [27, 28, 29•]. The role of cervical spondylosis in this context is sub judice [30].
4. Migraine drugs such as ergotamine and triptans are ineffective.
5. Further evidence against a "migrainous" background is the observation that pregnancy transitorily reduces the number of migraine attacks in migraine, whereas in our series only 1 of 14 CEH patients experienced any definite effect of pregnancy upon headache ($P<0.0001$ [chi-squared test]).

A detailed account of therapy is outside the scope of this communication. Suffice it to mention the following: Therapy, in whichever field of pain, must be designed according to intensity and the degree of chronicity of the pain. This also goes for CEH, where pain generally is only moderate; conversely, there is a clear tendency toward chronicity of the pain. This combination makes the therapeutic situation somewhat delicate. One would not be inclined to use "drastic" measures in general, due to the leniency of the pain. Such measures would be applicable only in the worst cases. On the other hand, applying a therapy, the effect of which must be assumed to last only weeks/months, may seem rather purposeless/perspectiveless in a chronic/close-to-chronic pain disorder.

A great variety of therapeutic approaches have been tried: analgesics, blockades, radiofrequency therapy, neurolysis ("liberation operations"), etc., almost invariably with only marginal and transitory effect. In recent years, in the more stubborn cases, invasive therapy (eg, stabilization operations in the neck) has been carried out [27, 28, 29•], with promising results. Extracranial electrical stimulation also has been used recently, but only preliminary results exist.

Conclusions

The pain situation in a CEH patient is a dynamic one, with a varying threshold for pain. CEH is probably one of the large headache groups. There are other headaches that also originate in the neck, such as neck-tongue syndrome [31], where headache may be an integral part of the picture [31, 32]. Workable criteria have been issued by the Cervicogenic Headache International Study Group [10]. These criteria have been validated [9•, 33, 34] and their reliability tested [35]. Criteria issued by the International Headache Society [36] unfortunately need a heavy overhaul before being impeccable [37, 38]. In these criteria, facial pain is, for example, not distinguished from head pain. Nor is a clear distinction made between neck pain and head pain. According to these criteria, a head pain apparently does not have to be present. Regarding therapy, we may be seeing some light at the end of the tunnel.

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Chapter 43

Hemicrania continua

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Hemicrania continua (HC), like chronic paroxysmal hemicrania (CPH), is an indomethacin-responsive headache. While other unilateral headaches accompanied by local autonomic phenomena are intermittent, short-lasting headaches, HC is characterized by a continuous course. HC varies in intensity, but in the form observed in practice, it does not usually disappear entirely. HC was first described by Sjaastad and Spierings (1984). Since that initial description, more than 130 cases have been described.

EPIDEMIOLOGY

Neither the incidence nor the prevalence of HC is exactly known. Generally, HC has been regarded as a rare syndrome; however, some headache clinics that have systematically searched for HC have reported a considerable number of patients; this suggests that the condition may be underdiagnosed (Peres et al., 2001; Wheeler et al., 2001). The fact that HC was not detected among 1838 parishioners in Vågå (Norway) shows that there are limitations to this term. There is a female preponderance: the sex ratio is approximately 2.4:1 female to male. Age of onset varied between 19–58 years, with a mean of 35.2 years (Bordini et al., 1991). The range may probably be wider.

CLINICAL FEATURES

HC is basically a continuous headache; HC is also in principle a unilateral headache (Sjaastad and Spierings, 1984). In unilateral headaches, there is a minor tendency to bilaterality, e.g., in CPH about 1%. One case of bilaterality (Pasquier et al., 1987) and a couple of cases of side-shift that have been described (Newman et al., 1992) seem acceptable. These occasional exceptions should be regarded as oddities. The forehead and temporo-orbital area are the principal sites of pain, although any part of the head can be affected (Bordini et al., 1991). Typically, the pain is mild to moderate in intensity. Pain quality is dull, aching, or pressing. Usually, exacerbations are superimposed upon the continuous pain. Exacerbations can last 20 min to several days. Nocturnal exacerbations can be mistaken for cluster headache or hypnic headache. Exacerbations may be associated with cranial autonomic and migrainous features.

Local autonomic symptoms, mostly ipsilateral lacrimation and conjunctival injection and nasal stuffiness (Bordini et al., 1991), are present in approximately one-third of HC patients but are not as prominent as in cluster headache or CPH. Migrainous features (photophobia, phonophobia, nausea, and throbbing) are common during exacerbations. Migrainous visual aura occurred in association with exacerbations of HC (Peres et al., 2002). There is a paucity of precipitating factors: menses and alcohol have been mentioned (Bordini et al., 1991). Neck movements do not trigger exacerbations, although occipital tenderness has been claimed to be present in about 70% of patients (Newman et al., 1994; Peres et al., 2001). These are apparently uncontrolled data.

The extent to which cervicogenic headache (CEH) is intermingled with HC is unknown (Sjaastad et al., 1993). Primary stabbing headaches may occur (41%), predominantly during the exacerbations (Peres et al., 2001). This figure should be compared with the figure of 35% in the general population (Sjaastad et al., 2001). The diagnostic criteria of HC according to the International Classification of Headache Disorders (ICDH-II: Headache Classification Committee of the International Headache Society, 2004) are presented in Table 43.1. It is worrying that our first case (Sjaastad and Spierings, 1984) would not have been recognized if "the autonomic features section" of the criteria had

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Table 43.1

Diagnostic criteria for hemicrania continua according to the International Classification of Headache Disorders, 2nd edition (Headache Classification Committee of the International Headache Society, 2004)

A. Headaches for >3 months fulfilling criteria B–D
B. All of the following characteristics:
   1. Unilateral pain without side-shift
   2. Daily and continuous pain without painfree periods
   3. Moderate intensity, but with exacerbations of severe pain
C. At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain
   1. Conjunctival injection and/or lacrimation
   2. Nasal congestion and/or rhinorrhea
   3. Ptosis and/or miosis
D. Complete response to therapeutic doses of indomethacin
E. Not attributed to another disorder

existed at the time. In other words, the criteria have regrettable shortcomings.

PATHOGENESIS

Matharu et al. (2004) demonstrated activation of the contralateral posterior hypothalamus and ipsilateral dorsal rostral pons in indomethacin-sensitive HC ($n = 7$). There are several issues that remain unresolved in the understanding of HC and similar headache pathophysiology. To the best of our knowledge, it has not been demonstrated where indomethacin or active metabolites have their effect in the central nervous system. Cerebrospinal fluid in the dog contained much lower concentrations of radioactivity after labeled indomethacin administration than plasma. The same was true in 1 human subject (Hucker et al., 1966).

Orbital phlebography ($n = 10$), blockades of the greater/minor occipital and supraorbital nerves ($n = 7$), and forehead sweating were all without gross pathology. Pupillometry did not show any gross abnormalities of sympathetic function (Antonaci, 1998). Quantification of lacrimation, nasal secretion, and salivation ($n = 2$) showed no asymmetries (Sjaastad et al., 1984b). End-tidal carbon dioxide monitoring and vagal nerve function tests ($n = 2$) were normal. Corneal indentation pulse amplitudes showed a slight asymmetry (>15%; S>NS) in 1 patient, whereas intraocular pressure was normal in both (Sjaastad et al., 1984).

TEMPORAL PATTERN

Like cluster headache and CPH, HC can also be classified in an episodic and chronic form. HC is frequently primary chronic. Prior to the chronic stage, there may be a recurrent stage, observed already in our third case (Sjaastad and Tjörstad, 1987). Although 10 of 18 HC patients had started out with a recurrent pattern, only 2 remained in this stage at examination (Bordini et al., 1991; Sjaastad and Antonaci, 1993). A transition from chronic to remitting stage has also been observed (Pareja, 1995). Some patients may continue in a remitting stage for a long period.

SECONDARY HEMICRANIA CONTINUA AND ASSOCIATED DISORDERS

C7 root irritation caused by a cervical disc herniation seemed to have aggravated the condition in one case (Sjaastad et al., 1995). A patient with human immunodeficiency virus (HIV) developed HC, by chance or not (Brilla et al., 1998). A patient in whom the indomethacin response faded after 2 months proved to have a mesenchymal tumor in the sphenoid bone (Antonaci and Sjaastad, 1992). Patients with escalating indomethacin requirement or loss of efficacy should be re-evaluated (Sjaastad et al., 1995). Two patients got secondary HC after internal carotid artery dissection (Rogalewski and Evers, 2004).

In 8 cases of "posttraumatic HC," the temporal relationship between trauma and HC onset was variable (Lay and Newman, 1999). Cases of HC with aura and side-shift of pain (Peres et al., 2006); migraine with aura, transformed into HC with aura (Palmieri et al., 2004); HC originating within the postpartum period (Spitz and Peres, 2004); HC with contralateral episodic cluster headache (Lisotto et al., 2003); HC evolved from episodic paroxysmal hemicrania (Castellanos-Pinedo et al., 2006); and a clinical picture resembling HC, but attributed to an unruptured saccular aneurysm (Vikelis et al., 2005) have been reported. Relating these constellations does not imply that we in any way commit ourselves as to the messages conveyed.

DIFFERENTIAL DIAGNOSES

Differential diagnoses of long-lasting unilateral headache include: (1) HC (primary and symptomatic forms); (2) so-called unilateral chronic migraine; (3) CEH; and (4) CPH and other similar headaches that can be associated with interictal, dull ache.

HC can be readily differentiated from unilateral chronic migraine by the responsiveness to indomethacin. Overuse of analgesics can generate a typical bilateral headache in HC. CEH is characterized by: (1) unilateral pain, initially in the neck/occipital region, the pain eventually radiating anteriorly; (2) precipitation/ aggravation of headache by neck movements/sustained uncomfortable neck posture or external pressure; (3) limitation of neck movements; and (4) discomfort in ipsilateral

neck and shoulder, none of which applies in HC. Moreover, the response to indomethacin is absolute in HC, not in CEH (Sjaastad et al., 1993). Various clinical features help to distinguish HC from CPH. First, in CPH exacerbations are short-lasting (2–45 min), whereas those in HC are longer-lasting. Secondly, the intensity in CPH is excruciating, whereas in HC it is moderate (or severe). A biological marker will be required to gain insight into how best to differentiate these syndromes (Antonaci, 1998).

INVESTIGATIONS

Diagnosis is based on clinical history, neurological examination, and a therapeutic trial of indomethacin. Cases of unilateral, chronic headache should have an indomethacin trial. Brain computed tomography and magnetic resonance imaging (MRI) of brain/cervical spine have demonstrated cervical degeneration changes, but no systematic, grave pathology. Four-vessel angiography has revealed no pathology ($n = 3$) (Bordini et al., 1991). An MRI brain scan is a reasonable screening investigation to exclude a symptomatic form of HC. If there is no response to indomethacin, further work-up should be carried out.

TREATMENT

Indomethacin is the drug of choice in HC as well as CPH. Sumatriptan is without effect in HC (Antonaci, 1998). Prophylatic therapy gives a prompt, complete, and enduring response. The effective dose of indomethacin ranges from 25 to 300 mg/day (Bordini et al., 1991). Dosage titration is necessary to cope with clinical fluctuations. Skipping or delaying doses may result in recurrence. "Indotest," i.e., indomethacin 50–100 mg intramuscularly, has been proposed as a diagnostic test for HC (Antonaci et al., 1998). The Indotest has the advantage that the diagnosis can be rapidly established, with complete pain relief occurring within 2 h. Indotest is likely to become the test of choice in chronic unilateral headache.

Concurrent treatment with gastric mucosa-protective agents is probably obligatory with courses of indomethacin of some length. Indomethacin does not exert any curative effect upon the basic disorder; it keeps the situation at bay, without any tachyphylaxis. Beside the indomethacin test, indomethacin discontinuation verification plays a crucial role for the diagnosis. The fact that the pain returns upon indomethacin discontinuation is a strong testimony, as regards HC, perhaps even stronger than that of the Indotest itself. It is only when this test is positive that the diagnosis can be considered as finally being established. If pain does not recur upon indomethacin discontinuation, this indicates that either: the pain has disappeared spontaneously, or: the diagnosis is wrong. In the first case, the HC may be in a recurring stage. Another indomethacin discontinuation test must then be carried out, during another bout, to verify the diagnosis. Cases to be reported in the future should follow this standard; they have not invariably done that in the past.

The site of action of indomethacin may be in the periphery or centrally. Kuritzky (1992) has described 4 cases of HC, non-responsive to indomethacin. Indomethacin response is an indisputable requirement in HC. The Kuritzky cases are accordingly unacceptable as HC; there is no proof for HC in Kuritzky's cases. One or more of them may have CEH. Since indomethacin response is a fundamental quality of HC, the Goadsby–Lipton proposal (1997) to accommodate indomethacin-negative cases is, therefore, beside the point. Indomethacin-resistant patients are not likely to be true cases of HC. Until the underlying pathophysiology of HC and the mode of action of indomethacin are better understood, it is prudent in clinical practice only to diagnose HC in patients with an unquestionable response to indomethacin.

There seems to have been a recent wave of revisionism, to the effect that HC was described in 1982, as "atypical cluster headache," a syndrome responsive to indomethacin (Diamond et al., 1982). Indomethacin response is a hallmark of the HC. HC is, according to Matharu et al. (2004), "exquisitely responsive to indomethacin." It is, therefore, highly surprising to know that only 50% of Diamond's cases showed a complete indomethacin response, and that in 17% there was no response at all. And with the most pure form of "background vascular headache" (solely together with "multiple jabs"), only 1 of 8 patients responded "excellently" to indomethacin. Unilaterality of headache is another characteristic of HC. In only 67% of the "atypical cluster headache" cases was there unilaterality – and even side-shift in 30%.

Other drugs reported to have been partially or even completely effective, frequently in isolated cases, include ibuprofen, piroxicam, betadextrin, naproxen, aspirin, the cyclooxygenase-2 inhibitor rofecoxib paracetamol with caffeine, and melatonin. Other non-steroidal anti-inflammatory drugs are generally less efficient than indomethacin. A positive response to verapamil was apparently observed in 2 patients and in 2 patients there was a response to topiramate (Matharu et al., 2005). Occipital nerve stimulation has been reported to improve pain in 1 case. This patient might not be a genuine case of HC (Schwedt et al., 2006).

NATURAL HISTORY AND PROGNOSIS

HC is a recently described disorder; its natural history is still being outlined. At this stage, it may seem to be a lifelong disorder in most cases. Patients should discontinue indomethacin at least every 6 months to ensure that they still have headache. The titrated dose should be the minimum effective one. Some patients prefer to use a rather low dosage and have a little pain, as a "sentinel" against overuse. The first case of HC described was treated with indomethacin for 19 years (Sjaastad, 2006). There was no tachyphylaxis, and intensity and other headache characteristic were unchanged.

As with CPH, patients with HC can thus expect an enduring response to indomethacin without developing tachyphylaxis. Almost a quarter develop gastrointestinal adverse effects (Pareja et al., 2001). Indomethacin does not seem to alter the long-term course; some patients experience a decrease in indomethacin requirement over time.

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SUNCT syndrome with paroxysmal mydriasis: Clinical and pupillometric findings

F Antonaci, G Sances, M Loi, G Sandrini, C Dumitrache and MG Cuzzoni

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SUNCT syndrome with paroxysmal mydriasis: Clinical and pupillometric findings

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Abstract

SUNCT syndrome (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) is a primary headache characterised by a high frequency of attacks associated with marked autonomic periocular signs and symptoms. Activation of the hypothalamus via the superior salivary nucleus is probably responsible for some of the autonomic involvement observed during SUNCT attacks. We describe a case of SUNCT with unusual autonomic features (e.g., mydriasis) and early onset. Pupillometric studies were performed both in a basal condition (without anisocoria) and after instillation of phenylephrine (a drug with direct sympathomimetic activity) and pilocarpine (a parasympathetic agonist). The findings in this patient seem to indicate involvement of the ocular sympathetic supply in SUNCT, responsible for the mydriasis, and seem to strengthen the possibility that the autonomic phenomena in this syndrome vary with different levels of pain severity.

Keywords

Autonomic features, pathophysiology, pupillometry, SUNCT syndrome

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Introduction

SUNCT syndrome (short-lasting unilateral neuralgiform headache attacks with conjunctival injection, tearing, sweating and rhinorrhoea) was first described by Sjaastad et al. in 1978 (1). Attacks of SUNCT, in which pain intensity is invariably greatest in the ocular/periocular area, are accompanied by marked unilateral autonomic activation and occur with a frequency of between three and 200 per day (1–3). Conjunctival injection and lacrimation are the most prominent autonomic features. Miosis on the symptomatic side has been described during pain but pupillometry has failed to show changes in pupil diameter (1,2,4), at least in the basal condition. Other associated cranial autonomic signs and symptoms may be present on the headache side: nasal blockage, rhinorrhoea, eyelid oedema, ptosis, hyperventilation, sweating or facial and ear flushing. Cohen et al. (5) mentioned one case of ipsilateral mydriasis, but gave no details.

Case report

A 22-year-old woman came to our observation with a one-year history of headache, but no family history of the disease. The clinical features of her headache suggested a diagnosis of SUNCT, and she indeed fulfilled the International Headache Society (IHS) diagnostic criteria (3), reporting short-lasting (3–5 minutes), left-sided attacks with ocular/periocular localisation of pain, occurring at a rate of 3–15/day and fluctuating in severity. In addition, she reported periodic mild background pain. The autonomic component of the attacks consisted of pronounced ipsilateral tearing and conjunctival injection. In addition, from the onset of the condition, the patient had also experienced concomitant (for the entire duration of the pain) transient pupillary dilation during severe/moderate attacks on the symptomatic side. Over the two months leading up to our observation, the headache had shown a pattern of 2–3 severe attacks/day accompanied by autonomic signs and symptoms and 10–20 mild-to-moderate attacks/day;

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with both types of attack there was clear-cut paroxysmal mydriasis, conjunctival injection and tearing on the symptomatic side (Figure 1).

One month before the patient came to our observation, she had also started experiencing, occasionally, short-lasting (1–5 minutes) episodes of scotoma coinciding with severe pain attacks and paroxysmal mydriasis. These episodes were described as the appearance of a grey spot in the centre of the field of vision, followed by luminous zigzag lines. The patient reported no photophobia, phonophobia or nausea.

The neurological examination was normal, as were the results of a series of other examinations: echographic Doppler ultrasound of the supra-aortic vessels, transcranial ultrasound, visual evoked potentials (VEPs), magnetic resonance imaging (MRI) and angio-MRI of the brain.

The indomethacin test (100 mg IM)(6), administered twice interictally, had no effect on attacks or on autonomic signs/symptoms.

The patient had previously used nimesulide to treat the pain, but without benefit. After an ophthalmological examination, she was put on 0.3% tobramycin (eyedrops) three times a day and ketorolac 10 mg on demand for five days; this regime led to the disappearance of the transient scotomas. The patient was prescribed topiramate (150 mg/day) and obtained a significant reduction in the number both of severe attacks and of episodes with paroxysmal mydriasis. After six months, topiramate was reduced to 100 mg/day because of weight loss (13 kg), hair loss and the progressive appearance of other side effects (a sense of 'shaking objects' in the symptomatic eye, mental slowing, dysphasia). After a year, topiramate was withdrawn and replaced with lamotrigine 100 mg/day. On this dosage, the patient had 1–2 short-lasting attacks/week associated with mild autonomic signs and symptoms. From November 2008, because of daytime somnolence and difficulty concentrating, oxcarbazepine 900 mg/day was introduced, while the lamotrigine was reduced to 75 mg/day. According to the headache diary kept by the patient, this modification of her therapy led to a reduction in the frequency and duration of the attacks.

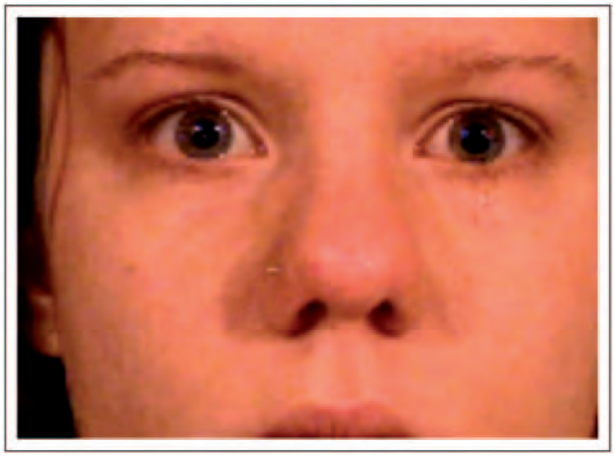

Figure 1. Anisocoria with mydriasis on the symptomatic (left) side.

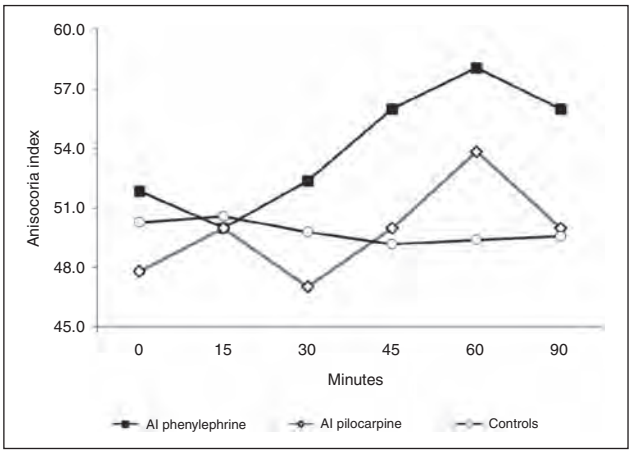

Figure 2. Pupillary measurements in SUNCT. Anisocoria index (AI): 100*(symptomatic side/symptomatic side + non-symptomatic side).

A pupillary evaluation was carried out to compare the response to sympathomimetic and parasympathomimetic agents.

Pupillary studies

In evaluating this patient, we used a 5.0 megapixel Sony digital camera to estimate mean pupillary diameters (vertical and horizontal). The measurements were taken both in the basal state and after topical stimulation with a sympathomimetic agent (phenylephrine [1%]), an agonist which acts directly on postsynaptic receptors in the dilatator muscle of the iris, and with a parasympathomimetic agent (pilocarpine [2%]). Pupillary dilation was measured at set intervals, comparing the responses of the symptomatic (S) and non-symptomatic (NS) sides. The anisocoria index (100* symptomatic side/symptomatic side + non-symptomatic side) was used for these calculations (7). It would also be interesting to study the response to alpha- and beta-blocking agents and indirectly acting sympathomimetic agents (hydroxyamphetamine, cocaine, tyramine), but these were not available in our setting. Absolute values in millimetres were not used for the calculation due to the relatively low resolution of the camera. The anisocoria index gives results that reflect more closely the clinical situation (Figure 2).

In the basal condition, there was no clear tendency to anisocoria. After phenylephrine administration, an overreaction (prominent anisocoria documented by an

increased anisocoria index) was observed on the symptomatic side. Pilocarpine administration resulted in a symmetrical reduction in pupil size with no significant difference emerging between the symptomatic and non-symptomatic sides, with the sole exception of the value at 60 minutes. On comparison of the patient's values with historical case data (7), the anisocoria index emerged as clearly asymmetrical from 45 to 90 minutes after phenylephrine instillation (Table 1).

Discussion

Sophisticated neuroimaging provides evidence that the posterior hypothalamus is involved in the pathophysiology of SUNCT, as is also suggested by the finding that it shares clinical characteristics with other headaches such as cluster headache (CH) and chronic paroxysmal hemicrania (CPH) (8); this hypothesis is further supported by evidence from functional imaging and deep brain stimulation studies (9). It has also been suggested that the pathophysiology of SUNCT, CH and CPH revolves around activation of the trigeminal-autonomic reflex (8), which consists of a brainstem connection between the trigeminal nerve and facial (VII cranial nerve) parasympathetic outflow. Benjamin et al. (10) have suggested that the prominent cranial autonomic symptoms that we encounter in these syndromes may be due to a central disinhibition of the trigeminal-autonomic reflex by the hypothalamus. Experimental data in rats show the existence of direct hypothalamic-trigeminal connections (11) and corroborate the idea that the hypothalamus exerts a modulatory role on nociceptive and autonomic pathways, specifically the trigeminovascular nociceptive pathway (12). The autonomic picture may be more complicated in SUNCT, whose impressive set of local autonomic signs (conjunctival injection, lacrimation, rhinorrhoea) are probably due to additional recruitment of the parasympathetic system.

The pupillometric findings described in this case of SUNCT seem to indicate involvement of the ocular sympathetic supply, possibly responsible for the mydriasis, and to strengthen the possibility that the autonomic phenomena in this syndrome may vary according to different levels of pain severity. It might be suggested that the key feature of trigeminal autonomic syndromes such as SUNCT is the severity of their expression and not the presence per se of autonomic dysfunction (13). Fanciullacci et al. (14,15) demonstrated impaired pupillary sympathetic responses in CH patients between attacks, within cluster periods. A comparison of CH patients with a relatively large control series showed that the pupil on the symptomatic side frequently, though not always, has a Horner-like appearance in CH (7,16). In the presence of unilateral lesions of the postganglionic sympathetic nerve fibres to the pupil, the affected pupil will, upon direct sympathetic stimulation, dilate more because of denervation hypersensitivity. Fanciullacci et al. (17) suggested that adrenergic transmission may be disrupted in headache sufferers generally, hypothesising a deficiency of noradrenaline in the iris adrenergic nerve terminals. The third neuron also exhibited reduced capacity of neurotransmitter synthesis and adrenoceptor hypersensitivity (17).

The results we obtained in this case with the available pupillary tests are consistent with sympathomimetic stimulation during the attack; however, there was a difference in response between the two eyes. If the origin of the stimulus is 'central', this could be due to a difference in stimulation magnitude.

However, the underlying mechanism is, in all probability, much more complex than simple stimulation of the parasympathetic or sympathetic nervous system suggest.

This issue aside, this patient nevertheless appears to be a genuine case of SUNCT with additional clinical features: paroxysmal mydriasis and transient scotoma episodes. Parasympathetic block and/or sympathetic stimulation, when separately used, produce a mydriatic response and might result in the clinical expression of a mydriatic eye. Our data in this SUNCT patient seem to raise more problems than they solve; in CH, on the other hand, the pupillary reaction is more consistent and easier to interpret (16).

Table 1. Pupillary measurements after phenylephrine and pilocarpine instillation[a]

Time (minutes)	0	15	30	45	60	90
AI phenylephrine	51.9	50.0	52.4	56.0	58.1	56.0
AI pilocarpine	47.8	50.0	47.1	50.0	53.8	50.0
Controls	50.3	50.6	49.8	49.2	49.4	49.6

[a]The patient was drug-free at the time of the test. AI (anisocoria index): 100*(symptomatic side/symptomatic + non-symptomatic side).

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ORIGINAL

Guidelines for telematic second opinion consultation on headaches in Europe: on behalf of the European Headache Federation (EHF)

José Pereira-Monteiro · Maria-Magdalena Wysocka-Bakowska · Zaza Katsarava · Fabio Antonaci

Received: 7 February 2010 / Accepted: 25 March 2010

Abstract The seeking of a second opinion is the long-established process whereby a physician or expert from the same or a similar specialty is invited to assess a clinical case in order to confirm or reject a diagnosis or treatment plan. Seeking a second opinion has become more common in recent years, and the trend is associated with significant changes in the patient-doctor relationship. Telemedicine is attractive because it is not only fast but also affordable and thus makes it possible to reach highly qualified centres and experts that would otherwise be inaccessible, being impossible, or too expensive, to reach by any surface transport. In Europe, the European Headache Federation (EHF), being able to draw on a group of headache experts covering all the European languages, is the organisation best placed to provide qualified second-opinion consultation on difficult headache cases and to develop a Headache Medical Opinion Service Centre. The provision of good quality clinical information is crucial to the formulation of a valid, expert second opinion. This preliminary step can be properly accomplished only by the primary health care provider through the furnishing of an appropriate clinical report, together with the results of all available tests, including original films of all imaging studies already performed. On receiving the EHF's proposed standardised data collection form, properly filled in, we may be sure that we have all the relevant data necessary to formulate a valid expert second opinion. This form can be accessed electronically and downloaded from the EHF website. Once finalised, the EHF second opinion project should be treated as a pilot strategy that requires careful monitoring (for the first year at least), so that appropriate changes, as suggested by the retrospective analysis and its quality control, can be implemented.

Keywords Headaches · Guidelines · Telemedicine · Telematic · Second opinion · Consultation

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Introduction

The seeking of a second opinion is the long-established process whereby an expert from the same or a similar specialty is invited to assess a clinical case in order to confirm or reject a diagnosis or treatment plan. A second opinion might be requested by the primary physician (primary health care provider, PCP), by the patient, or by the patient's relatives. It serves to reduce uncertainty and thus anxiety, and to promote a better understanding of the disease by the patient and her/his family, as well as better compliance with the treatment plan. When a second opinion confirms the initial diagnosis, it may indeed provide

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reassurance and help the patient to accept her/his disease [1].

By bridging an important gap between the primary physician's diagnosis and treatment plan and the patient's emotional need for expert opinion, a medical second opinion should thus help to establish a patient's medical needs and contribute to achieving optimal treatment goals.

Because traditional second opinion evaluations involve a face-to-face examination, they can be difficult to obtain, rather expensive and involve a delay; as a result, they tend to be carried out in very few or very special cases.

However, in recent decades, advances in the field of information technology, and in telecommunications technology in particular, have led to the development of a new model of second opinion and the creation of the concept of telemedicine.

Nowadays, with access to the internet so widespread, patients and doctors are directly involved in establishing primary diagnoses and in the treatment decision-making process. Both categories actively use the internet to get information about a disease and about modern treatment options and strategies and will often actively seek second opinions from opinion leaders in the field.

Initially, telemedicine (the use of telecommunications technology for medical diagnosis and patient care) was mainly used for getting second opinions on imaging data (e.g. radiological and neuroradiological images, online ECG, USG, etc.). However, this novel concept rapidly spread to other medical specialties: pathology, surgery, cardiology, dermatology, orthopaedics, gynaecology, urology, neurology, including neurosurgery and so on [2–4].

Telemedicine [5] has proved attractive because it is not only fast but also affordable and thus makes it possible to reach highly qualified centres and experts that would otherwise be inaccessible (unavailable, impossible or too expensive to reach by any surface transport) [2, 5, 6].

As a result of this trend, which is one of the reasons why second opinion seeking has become more common in recent years, the relationship between patients and doctors has changed radically: the era of the paternalistic relationship, in which patients blindly followed the advice of their doctors, is over.

The European Headache Federation project

In the field of headache medicine in Europe, the European Headache Federation (EHF), being able to draw upon the expertise of a group headache experts covering all the European languages, is the organisation best placed to provide qualified second opinion consultation on difficult headache cases. Through its development of a Headache Medical Opinion Service Centre, the EHF will provide a valuable and necessary service to the populations and health care providers of all European countries, while also accomplishing the most important of its aims: to promote headache knowledge and care in Europe [7–9].

The provision of good quality clinical information is crucial to the formulation of a valid, expert second opinion. This preliminary step can be properly accomplished only by the PCP through the furnishing of an appropriate clinical report, together with the results of all available tests, including the original films of all imaging studies already performed.

Furthermore, it may be better accomplished if a standard data collection form is provided in advance. To this end, several second opinion software solutions have been developed to facilitate communication and prevent the omission of important, sensitive data, while guaranteeing adequate personal data protection [6].

To the best of our knowledge, no such software programs are available for the requesting and formulation of second opinions on headache patients, even though there is a need for them in order to guarantee optimal results. When assessing a difficult case, there are certain crucial data that must always be collected. First of all, it is important to know the reason for the consultation: whether it is to confirm a diagnosis, for differential diagnosis or diagnostic work-up counselling, or for treatment advice. The need for treatment advice may arise when a patient fails to respond to a therapy or develops side effects, or it may simply stem from a desire to explore all possible and available therapeutic options in order to optimise a patient's treatment.

The expert should also know who is requesting the second opinion: whether it is the patient her/himself, family members and/or friends, or a doctor (i.e., the PCP). If it is the PCP, it is important to know his/her name, affiliation and contact details in case he/she needs to be contacted again in order to get more detailed clinical information.

The best way to provide the necessary information is through a semi-structured questionnaire. The data collection form (available as Electronic Supplementary Material) must cover a series of important aspects, as detailed in the following steps:

1. Patient identification (name/initials, gender, birth date/age, country/nationality, language);
2. A brief present disease (headache) history including
    a. Headache characteristics (type 1,2,3 or more), date of onset, location (unilateral, side shifting, bilateral), quality of pain (pulsating, tightening, stabbing), whether headache worsens with physical activity, the presence of aura symptoms (visual, sensory, motor) and associated symptoms

(phonophobia, photophobia, nausea or vomiting), as well as dysautonomic symptoms (red eye, tearing, rhinorrhoea, pacing around) or basilar artery symptoms (diplopia, vertigo, tinnitus, hypoacusia, ataxia), or any others.

b. It is also important to indicate the temporal pattern of the headache using the temporal definitions given in the IHS criteria [10] (acute/episodic; subacute/progressive; chronic paroxysmal or continuous), as this aspect may be difficult to establish without a clinician's contribution.

3. Details of the patient's previous medical history, particularly with regard to comorbid psychiatric and internal diseases and the medications used to treat them. This information is very important, and should always be available.
4. Family medical history, as well as social and professional background and habits. This information, too, can be highly relevant.
5. A full clinical examination. It is crucial to have an overview of the patient's clinical conditions, including the results of general and neurological examinations (mental status, cranial nerves, motor system, reflexes, sensory and cerebellar system evaluation), but the quality of this overview will depend on the quality of the clinician information provided.
6. Results of diagnostic work up, namely of

- Blood laboratory tests: haematology, biochemistry, immunology and serology, (ESR, CRP);
- Neurophysiological examinations (EEG, EMG or EP) and echo-Doppler, USG, transcranial-Doppler of extracranial (carotid, vertebral) and intracranial vessels,
- Neuroimaging studies (CT, MRI, or ANGIO MRI), when advisable and available.
- All other evaluations, including, for example, cardiological, ophthalmological and ENT consultations.

It is also important to know the suggested clinical diagnosis (headache type or types), as formulated by the PCP, as well as the patient's other current comorbid medical conditions.

Information should be given regarding current headache treatments (prescribed and over-the-counter medications) for acute and for prophylactic therapy (drugs, doses, treatment duration, response and side effects). Use/overuse of OTC drugs and/or other substance use or abuse should be reported, as should treatments used for other comorbidities [8].

On receiving this proposed standardised form, properly completed, we can be sure that all the relevant data have been provided, and a better result, in terms of a valid expert second opinion, may thus be expected [11, 12]. The proposed application form can be accessed electronically and downloaded from the EHF website, automatically translated into the user's language, thereby facilitating communication [8, 9, 11, 12].

The authors of the present document can be contacted for consultations on behalf of the EHF, but other experts in the field are also welcome to compose a list of opinion leaders on the field (Board of Headache European Consultants) that can provide the requested second opinion, If possible, with the same language of the informer, with quality and safety using appropriate telecommunicating technology [11] (i.e. telecommunication or Skype connection).

Through this project, the EHF will open the way for better care for patients with difficult or rare headache conditions, and also for people from remote and/or small places where health care facilities are more restricted and gaining access to a headache expert can be difficult.

Through modern telecommunications technology and internet teleconsultation, the EHF might thus be enabled to accomplish, on a global level, its mission to provide strong medical expert support in the field of headache.

The objectives the EHF aims to achieve through the implementation of this service are:

1. Secure and fast access to patient information, wherever the patient is located, also making use of on-line dialogue methods (i.e. Skype);
2. better quality diagnosing and treatment;
3. reduced time to treatment;
4. reduced use of OTC drugs;
5. promotion of more efficient use of resources; and
6. promotion of on-line collaboration among health care professionals (across health care organisations and national borders).

Once finalised, the programme should be treated as a pilot strategy and be carefully monitored (for the first year at least), so that appropriate changes, as suggested by the retrospective analysis and its quality control, can be implemented.

The main problem this project could encounter, in the event of a large volume of requests, is that of the costs involved. It is important to estimate these, i.e., the total cost of implementing the project, as well as the costs per case. It is also essential to establish how these costs will be met (who will pay) and to secure the funds needed. The success of the project will also depend on the availability of a good programme, software and informatics with a broadly available platform.

Therefore it is necessary to consider all the possible sources of funding, asking as to whom we should look to for the necessary grants and financial support: the EHF, the

WHO, local health authorities, the pharmaceutical industry, or private companies.

Since the EHF is a non-profit organisation, which seeks to accomplish a mission and pursues prestige rather than financial gain, this reduces the total costs of the programme and should make it possible to obtain financial support from an external sponsor.

A further consideration is the legal question of the liability and responsibility of the consulting experts offering diagnoses and proposing treatments. The expert second opinion they provide should be presented and considered purely as advice, making it quite clear that full responsibility cannot be accepted for advice given on the basis of information provided by a primary health physician. This issue, however, needs further discussion and clarification.

Conflict of interest None.

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EXPERT REVIEWS

Almotriptan for the treatment of acute migraine: a review of early intervention trials

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Almotriptan is a serotonin (5-hydroxytryptamine)$_{1B/1D}$ receptor agonist (triptan) that has shown consistent efficacy in the acute treatment of migraine with excellent tolerability. It is an effective, well-tolerated and cost-effective triptan, as demonstrated by improvement in rigorous, patient-orientated end points, such as 'sustained pain-free without adverse events'. Results from *post hoc* analyses, observational studies and well-controlled, prospective clinical trials have shown that significant improvements can be achieved if almotriptan 12.5 mg is administered within an hour of migraine onset, particularly when pain is mild, rather than waiting until pain is moderate-to-severe. Benefits were also achieved with early treatment of moderate-to-severe pain. Time-to-treatment was the best predictor of headache duration, whereas initial headache intensity best predicted most other efficacy outcomes. Early administration of almotriptan 12.5 mg not only produced rapid symptomatic relief, it also improved the patient's quality of life and ability to resume normal daily functioning. Furthermore, the efficacy of almotriptan is not significantly affected by allodynia (purported to reduce the efficacy of triptans). Thus, the excellent efficacy and tolerability profile of almotriptan administered early in a migraine attack indicate that it may be a first-line treatment option in this common, underdiagnosed and undertreated disorder.

KEYWORDS: allodynia • almotriptan • early treatment • migraine

Background

Migraine is a common, chronic, disabling, neurovascular disorder. The WHO estimates that there were over 324 million migraine sufferers across the globe in 2005, including more than 77 million in Europe [1]. Migraine is characterized by attacks of headache pain in the presence of one or more migraine-associated symptoms, such as nausea and/or vomiting, photophobia and phonophobia, and with or without aura, which usually comprises visual and/or sensory and/or speech disturbances [2]. Although the etiology of migraine is not fully understood, it is believed to be associated with the release of vasodilatory neurotransmitters by the trigeminovascular system, vasodilation of the intracranial extracerebral blood vessels and increased nociceptive neurotransmission [3]. Migraine not only impacts the patient in terms of disease morbidity and reduced quality of life, it is also a burden on society as a result of the high rates of disability and loss of productivity. Indeed, the WHO ranks migraine as one of the most disabling disease states (disability class VII on a scale of I–VII), placing it in the same class as active psychosis, quadriplegia and terminal-stage cancer [1]. The net result is a significant financial burden on healthcare resources, and in terms of direct and indirect costs migraine is estimated to cost the European community €27 billion per year [4].

Migraine treatment generally ranges from over-the-counter analgesics (including NSAIDs such as ibuprofen) to specific acute migraine treatments, such as ergotamine (an ergot derivative that was the first class of specific agents for the acute treatment of migraine) and the serotonin (5-hydroxytryptamine)$_{1B/1D}$ receptor agonists (commonly known as the triptans) [5–8]. The introduction of the triptans revolutionized the acute treatment of migraine. They are highly effective, as evidenced by the results of numerous well-controlled clinical trials [6,7]. They exert their effects by selectively stimulating the 5-hydroxytryptamine$_{1B/1D}$ receptors in the cranial arteries and trigeminal nerves, resulting in inhibition of the release of vasodilatory neurotransmitters and inhibition of nociceptive

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neurotransmission and also constriction of painfully distended intracranial extracerebral vessels [3]. In controlled clinical trials, patients with migraine were initially instructed to take triptans when the severity of their headache pain was moderate-to-severe [8]. There were many reasons for this, such as allowing migraine pain to be distinguished from nonmigraine headache (e.g., tension-type headache) and providing a higher baseline level of pain against which to measure change and to minimize the influence of a placebo response [8]. However, in everyday practice some patients with disabling migraine treated their headache when the pain was mild to prevent progression to moderate-to-severe pain and to minimize migraine-related disability [9]. Conversely, in clinical trials, some patients who had been instructed to treat the pain when it was mild, delayed treatment until it reached moderate-to-severe intensity [10,11], possibly owing to a fear of adverse events [12]. Historically, the main goal for migraine treatment was to relieve moderate-to-severe pain and this was reflected in the protocols of early clinical trials. However, in recent times the goals of migraine treatment have evolved based on patient requirements; patients want rapid pain relief and freedom from pain, the restoration of normal functioning, a reduced risk of recurrence and all this in the absence of adverse effects [13]. These requirements have led to the inclusion of more patient-orientated end points in clinical trials, and they also raised the question concerning the optimal timing of treatment in order to achieve maximum benefit.

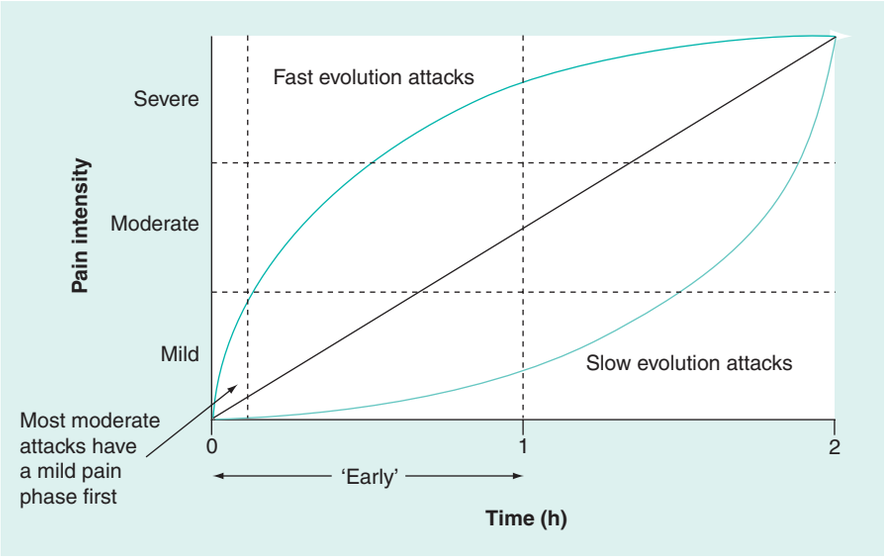

Figure 1. The evolution of migraine pain.
Reproduced with permission from [9].

A growing body of clinical experience, as well as evidence from *post hoc* analyses, including the reasons why patients violated the protocol, and also a small number of well-controlled clinical trials designed to examine the impact of treatment timing on patient outcomes, reported that early treatment with triptans, when the pain was still mild, resulted in significantly improved pain relief [9]. Interestingly, early intervention was already standard practice with ergotamine [5]. More recently it has been proposed that early treatment may prevent 'central sensitization', which is an increase in responsiveness of central pain neurons manifesting as cutaneous allodynia (pain resulting from a non-noxious stimulus to normal skin) [14]. Indeed, a pivotal open-label study found that triptan therapy was more effective if initiated before the onset of cutaneous allodynia [15].

The evidence for the clinical benefits of early administration of almotriptan in a migraine attack, when headache pain is mild, is the subject of this review. It is estimated that 81–90% of migraine attacks begin with mild pain and then progress at varying rates to more severe forms of headache – within a few minutes to over 1 h (Figure 1) [16]. Therefore, the terms 'early' and 'mild' are not interchangeable and the end points of early or mild used in almotriptan studies are clearly defined when discussing its benefits.

Clinical studies with almotriptan

Almotriptan has been extensively studied in randomized, placebo- or active-comparator-controlled clinical trials and postmarketing surveillance studies, which more closely reflect everyday clinical practice since they include a wider range of patients with different medical histories (for detailed reviews see [17,18]).

The majority of early controlled clinical trials required patients to take the triptan when their migraine headache was of moderate-to-severe pain intensity, and the primary end point was pain relief at 2 h. In these studies, almotriptan was significantly superior to placebo at reducing pain at 2 h; furthermore, significantly more patients were pain-free as early as 30 min after treatment [19,20]. Almotriptan also significantly reduced the incidence of migraine-associated symptoms, including vomiting, photophobia and phonophobia, as well as the need for rescue medication [19,21]. Importantly, almotriptan has excellent tolerability, with a similar incidence of adverse events as placebo [19,22]. This important attribute of almotriptan identified in short-term studies was confirmed in long-term, open-label studies [23,24].

The use of placebo-controlled trials is a controversial but important issue. Indeed, the International Headache Society stated that trials investigating agents for the acute treatment of migraine should be carried out "in accordance with the principle of the Declaration of Helsinki" [25], that is, when an effective agent is available it is unethical to assign patients to a treatment known to be less effective. However, the same International Headache Society guidelines later explicitly recommended the use of placebo [2]. The placebo response in clinical trials of acute migraine treatments is known to be high and varies widely (6–47%); placebo has been shown to act on serotonin-dependent hormone secretion mimicking the effects of triptans [26]. It is therefore recommended that agents for the acute treatment

of migraine must be shown to be significantly more effective than placebo [25]. This has clearly been the case for almotriptan [17,18] and, furthermore, the incidence of adverse events with this agent has not been significantly different from rates reported for placebo [19,22]. The latter is important given the 'nocebo' effect – the association between placebo and adverse events [27]. Despite the controversy surrounding placebo-controlled trials, placebo-adjusted data enable the rigorous comparison of triptans across clinical studies [26].

Since the early controlled studies, a number of alternative end points, including 'sustained pain-free' (SPF; pain-free at 2 h, without recurrence or the need for rescue medication between 2 and 24 h), which may be more relevant to the patient, have been investigated. Meta-analyses of data from earlier studies demonstrated that almotriptan significantly increased the number of patients who achieved SPF status compared with placebo [19,28].

A further step to more closely reflect patient requirements for migraine treatment is the use of the end point SPF without adverse events (SNAE). A meta-analysis of data with the available triptans found that patients receiving almotriptan 12.5 mg had a significantly higher rate of SNAE compared with the other triptans evaluated and the authors attribute this to its excellent tolerability – the rate of adverse events with almotriptan was "30% lower than would be expected" [29]. Patients receiving almotriptan 12.5 mg also showed significantly higher rates of SNAE compared with ergotamine plus caffeine ($p < 0.05$) in a randomized, double-blind crossover trial [30]. A significantly greater proportion of patients were more satisfied with almotriptan 12.5 mg than with ergotamine plus caffeine ($p < 0.05$) in both arms of this crossover trial. Indeed, when stratified according to previous treatment with specific triptans, almotriptan was preferred by 81% of patients previously treated with naratriptan, 74% previously treated with sumatriptan, 72% previously treated with rizatriptan and 70% of those previously treated with zolmitriptan. Furthermore, based upon the findings of this trial physicians indicated that they would continue almotriptan therapy in 92% of patients.

Almotriptan in early/mild migraine

The efficacy of almotriptan in the treatment of migraine when the pain was still mild was retrospectively assessed in two large, long-term studies in which patients were instructed to take almotriptan 12.5 mg at the onset of a migraine attack of any pain intensity [31,32]. The results of these two analyses suggest that almotriptan used when headache pain was mild, before it became moderate-to-severe, consistently improved outcomes. Indeed, early intervention with almotriptan not only improved its efficacy, but also the speed of its therapeutic effect, and dramatically increased the probability of achieving SPF status (**Table 1**) [33].

A *post hoc* analysis of data from a European, 1-year, open-label study aimed to determine the benefits of almotriptan given when pain intensity was mild [31]. The original study included 762 migraneurs using almotriptan 12.5 mg for the treatment of migraine of any pain intensity. The *post hoc* analysis involved

Table 1. Efficacy of almotriptan when given for the treatment of migraine of mild intensity, before it reaches moderate-to-severe (not mild); results from *post hoc* analyses.

Study	Migraine pain intensity												Ref.
	1 h pain-free (%)			*2 h pain-free (%)*			*Recurrence (%)*			*Use of rescue medication (%)*			*Sustained pain-free (%)*			
	Mild	*Not mild*†	*p-value*	*Mild*	*Not mild*†	*p-value*	*Mild*	*Not mild*†	*p-value*	*Mild*	*Not mild*†	*p-value*	*Mild*	*Not mild*†	*p-value*	
Pascual and Cabarrocas	47	14	0.001	84	53	0.001	28	33	0.01	8	13	0.01		Not reported		[31]
Mathew	35	8	0.001	77	44	0.001	13	25	0.001	9	17	0.001	67	37	0.001	[32]

†Moderate-to-severe.
Adapted from [33].

118 migraneurs who had treated at least three mild and three moderate-to-severe attacks and aimed to determine the within-patient benefits of almotriptan. A total of 708 attacks were analyzed. By 1 h after almotriptan treatment, 47% of patients experiencing mild attacks were pain-free compared with 14% of patients with moderate-to-severe migraine ($p < 0.001$), and this increased to 84 and 53% at 2 h, respectively ($p < 0.001$). Indeed, the chance of being pain-free at 1 h for at least two out of the three attacks was 45% in those experiencing mild headaches and 9% for those with moderate-to-severe headaches, and this increased to 88 and 56% at 2 h, respectively. The incidence of recurrence was significantly lower in patients treating mild attacks (28%) compared with those with moderate-to-severe attacks (33%; $p < 0.01$), and significantly fewer patients required rescue medication (8 vs 13%; $p < 0.01$). Almotriptan was well tolerated, with an incidence of adverse events of 6 and 7% in those treating mild and moderate-to-severe attacks, respectively.

Similar results were obtained in a *post hoc* analysis of data from a 6-month study undertaken in the USA [22,32]. This analysis involved 582 migraineurs who treated 10,645 migraine attacks of any severity with at least one dose of almotriptan 12.5 mg [32]. Pain-free status was significantly higher in patients treating mild attacks compared with moderate-to-severe attacks at 1 h (35 vs 8%; $p < 0.001$) and at 2 h (77 vs 44%; $p < 0.001$). Again, recurrence rates were significantly lower in those taking almotriptan for a mild attack compared with a moderate-to-severe attack (13 vs 25%; $p < 0.001$) as was the need for rescue medication (9 vs 17%; $p < 0.001$). Furthermore, patients treating mild attacks were much more likely to reach SPF status compared with those treating moderate-to-severe attacks (67 vs 37%; $p < 0.001$). This is a dramatic result considering that SPF rates of 10–25% were achieved in placebo-controlled studies of triptans that were not initiated early (the highest SPF rate was reported with almotriptan 12.5 mg) [6]. Almotriptan was well tolerated in this 6-month study; nausea (3%) and dizziness (2%) were the most frequently reported drug-related adverse events.

A further *post hoc* analysis was undertaken to determine the value of triptans in the early treatment of moderate-to-severe migraine [34], using data from a 1-year double-blind study investigating the effect of time on triptan treatment (almotriptan and sumatriptan) clinical response [35]. This analysis showed that early treatment with almotriptan, even when pain was moderate-to-severe, improved overall efficacy, including the likelihood of achieving SPF status. The analysis involved patients who took almotriptan 12.5 mg (n = 95), sumatriptan 100 mg (n = 115) or placebo (n = 95) within 1 h of the onset of moderate-to-severe migraine (53% of the original study population). By 2 h after treatment 38% of those receiving almotriptan were pain-free ($p = 0.016$ vs placebo), as were 36% of those receiving sumatriptan ($p = 0.028$ vs placebo) and 19% of those receiving placebo. The mean 2-h pain-free rate following early treatment with almotriptan was also superior to that reported in the parent study, in which migraine was treated "when it became moderate-to-severe" [35]. SPF rates were 35% with almotriptan ($p = 0.022$ vs placebo), 30% with sumatriptan (not significant vs placebo) and 17% with placebo; there was no statistically significant difference between the almotriptan and sumatriptan groups. However, when these results were stratified according to baseline pain intensity (moderate or severe), significantly more patients receiving almotriptan for attacks of moderate severity were pain-free at 2 h and achieved SPF status than those receiving placebo ($p < 0.05$ for both). Furthermore, SPF rates were higher in the almotriptan early treatment group compared with the overall

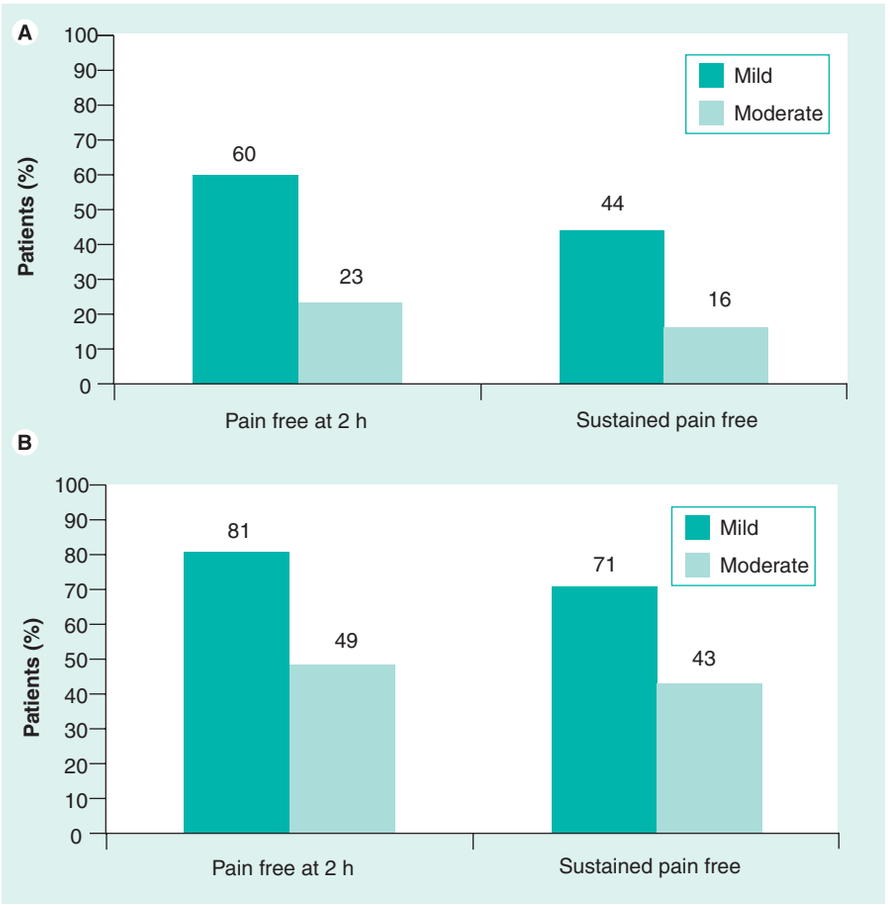

Figure 2. Percentage of patients pain-free at 2 h, and achieving sustained pain-free status in two observational studies (TEA 2000 and TEA 2001), reflecting routine clinical practice led by (A) neurologists and (B) primary care physicians.
Reproduced with permission from [38].

almotriptan group in the parent study, which was not the case for sumatriptan [34,35]. In the parent study, almotriptan 12.5 mg had a tolerability profile similar to placebo, whereas sumatriptan was associated with significantly more adverse events ($p < 0.001$ vs almotriptan 12.5 mg and placebo) [35].

Two large observational studies (Tolerability and Efficacy of Almogran® [TEA]) were undertaken in Spain to determine the efficacy and tolerability of almotriptan 12.5 mg in two routine clinical practice settings: neurology and primary care (TEA 2000 and TEA 2001, respectively) [36–38]. These studies confirmed the benefits of almotriptan documented in controlled clinical trials; namely placebo-like tolerability and rapid and sustained efficacy, particularly when administered early in an attack when the pain was mild.

In each study patients were instructed to report data on their migraine attacks for 3 months. Data from 4253 attacks were generated by 1643 patients recruited by 317 neurologists, and 4183 attacks by 2074 patients recruited by 640 primary care physicians. Patients taking almotriptan when the headache pain was mild achieved better pain-related benefits (pain-free at 2 h and SPF [Figure 2]) than those who waited until the pain was moderate-to-severe. Recurrence rates were low in both studies: 21% in the neurologist study and 11% in primary care. The incidence of adverse events was also low (3.9 and 1.1% in the neurology and physician studies, respectively), with chest pain occurring in only 0.2 and 0.1% of patients in each study, respectively, and cardiovascular symptoms in 0.4 and 0.1%, respectively.

Prospective studies

In order to definitively demonstrate the benefits of almotriptan for the early treatment of migraine and/or treatment when the pain is still mild, prospective well-controlled clinical trials have been undertaken.

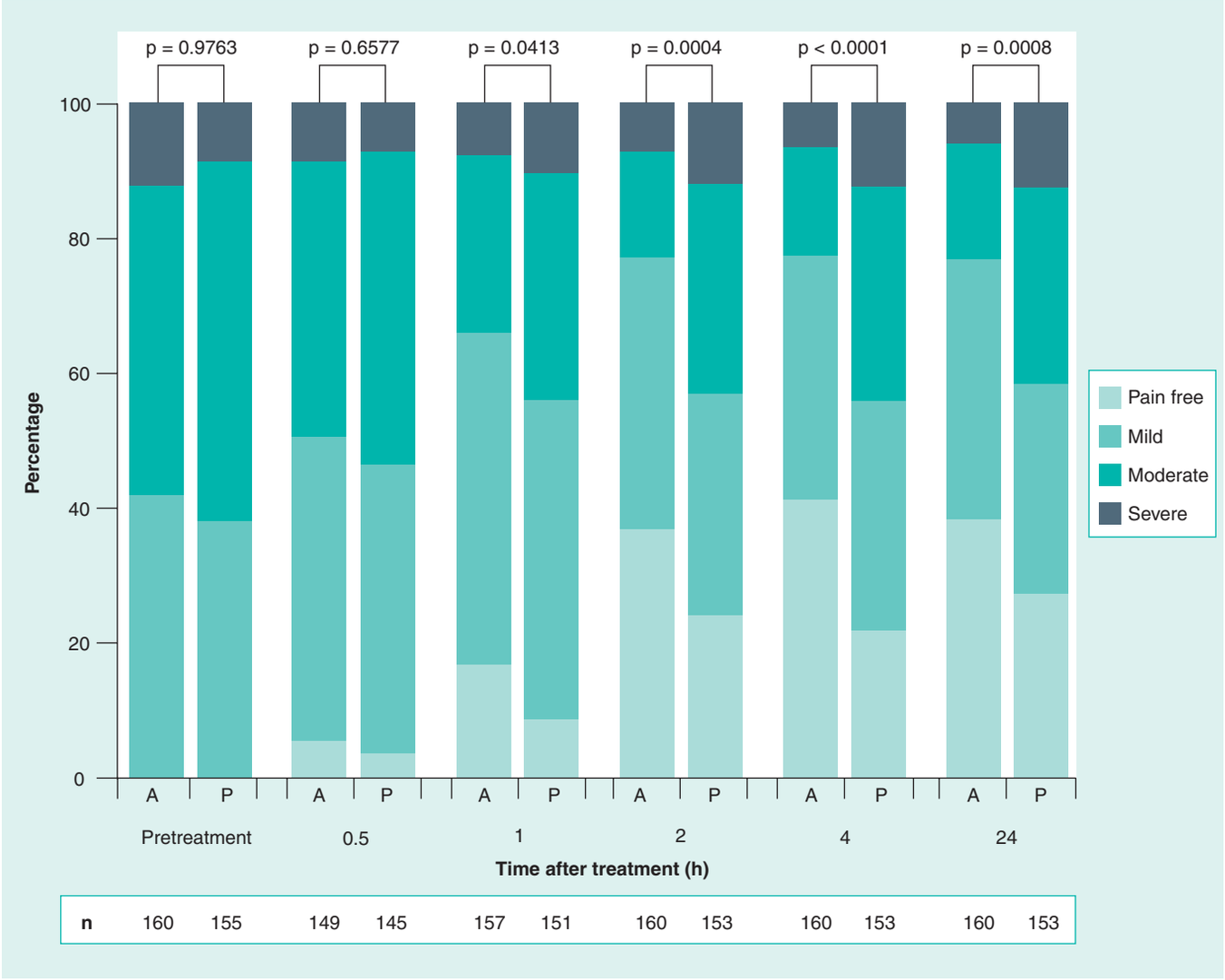

Figure 3. Pain intensity pretreatment and at various time points after early treatment of migraine (<1 h after onset) with almotriptan 12.5 mg or placebo in the Almotriptan Early Migraine Intervention Study (AEGIS).
Reproduced with permission from [40].

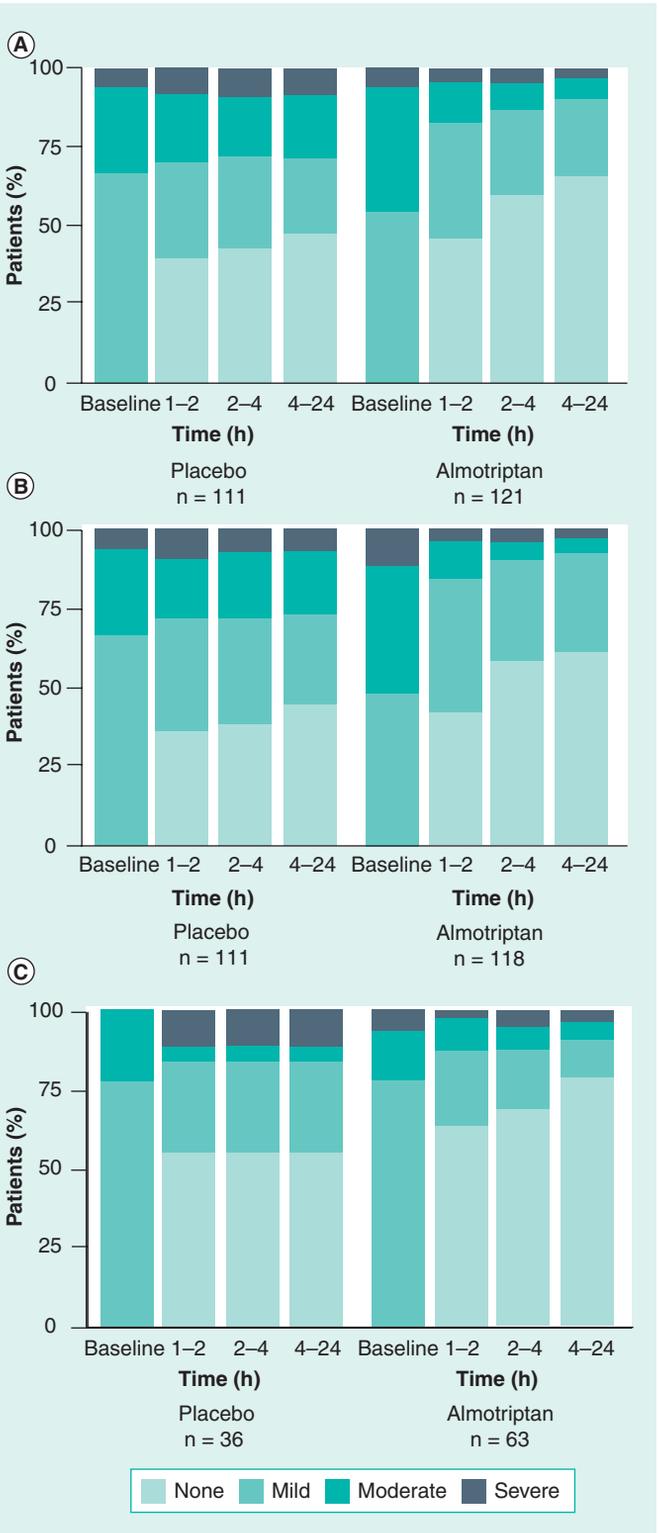

Figure 4. Severity of (A) phonophobia, (B) photophobia and (C) nausea at various time points after early treatment of migraine (<1 h after onset) with almotriptan 12.5 mg or placebo in the Almotriptan Early Migraine Intervention Study (AEGIS).
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The Almotriptan Early Migraine Intervention Study

The Almotriptan Early Migraine Intervention Study (AEGIS) was a prospective, multicenter, double-blind, placebo-controlled, parallel-group study that aimed to determine the efficacy and tolerability of almotriptan 12.5 mg for the acute treatment of three migraine attacks when administered within 1 h of headache pain onset regardless of pain intensity [39]. The effects of early treatment with almotriptan 12.5 mg on migraine-associated functional disability and quality of life in patients enrolled in this study were also assessed [40]. Almotriptan administered within an hour of pain onset for the first migraine was significantly more effective than placebo (Figure 3) [39,40]. Patients receiving almotriptan also had a significant reduction in pain intensity compared with placebo ($p = 0.0413$ at 1 h; $p = 0.0004$ at 2 h; $p < 0.0001$ at 4 h; and $p = 0.0008$ at 24 h). From 1 h to 24 h post-treatment there were more patients pain-free and fewer patients with severe pain in the almotriptan group compared with the placebo group. The pain relief produced by almotriptan was associated with a return to normal level of functioning: 77, 95 and 92% of all patients who were pain-free 0.5, 1 and 2 h after treatment of their first migraine attack were able to perform normal activities [40].

Almotriptan significantly reduced the intensity of phonophobia, photophobia and nausea 2–4 and 4–24 h after treatment ($p < 0.05$ for all), despite patients receiving almotriptan having a significantly higher incidence of phonophobia and photophobia at baseline ($p = 0.025$ and $p = 0.002$ vs placebo, respectively; Figure 4). These migraine-associated symptoms were associated with functional disability in patients ($p < 0.0001$ for each) [40].

For up to 4 h after treatment of their first migraine attack, patients in the placebo group required rescue medication at almost twice the rate of those treated with almotriptan (50 vs 28%; $p < 0.001$) [40]. Moreover, almotriptan reduced the need for rescue medication, compared with placebo, at all time points during the three migraine attacks, and significantly reduced the need for rescue medication over a 24-h period ($p = 0.0002$, $p = 0.039$ and $p = 0.039$ during attacks 1, 2 and 3, respectively).

Almotriptan was also associated with significant reductions in mean functional disability compared with placebo at 2 and 4 h post-treatment during attack 1 (Figure 5) [40]. Furthermore, during the three migraine attacks, almotriptan resulted in a higher level of normal functioning at all time points between 0.5 and 24 h, compared with placebo. This occurred despite the fact that patients in the placebo group took more rescue medication at 2 h. Almotriptan also resulted in a greater proportion of patients achieving a normal level of function at earlier time points compared with placebo across all three attacks (by 2 h for attacks 1 and 3 and by 1 h for attack 2). The likelihood of patients functioning normally was significantly greater for those treated with almotriptan compared with placebo in attack 1 at 2 h ($p = 0.0026$) and 4 h ($p = 0.0007$), in attack 2 at 1 h ($p = 0.0003$) and 4 h ($p = 0.0112$), and in attack 3 at 2 h ($p = 0.0448$). The return to normal function was associated with the absence of pain and migraine-associated symptoms. Treatment with almotriptan also resulted in better 24-h

Migraine Quality of Life Questionnaire (MQoL) scores during all three migraine attacks (Figure 6) [40]. In this study, almotriptan 12.5 mg had a tolerability profile similar to placebo. The safety analysis was undertaken in patients treating three migraines (almotriptan n = 174, placebo n = 173) [39]. The only adverse events that occurred at a frequency greater than 1% were somnolence (almotriptan n = 2, placebo n = 4), nausea (almotriptan n = 2, placebo n = 3), vomiting (almotriptan n = 2, placebo n = 1) and fatigue (almotriptan n = 2; placebo n = 0).

Overall, the results of the AEGIS have shown that early treatment of migraine with almotriptan 12.5 mg was well tolerated and significantly more effective than placebo. Importantly, its efficacy in reducing pain and migraine-associated symptoms when administered early allowed more patients to return to normal functioning a lot more quickly [39,40].

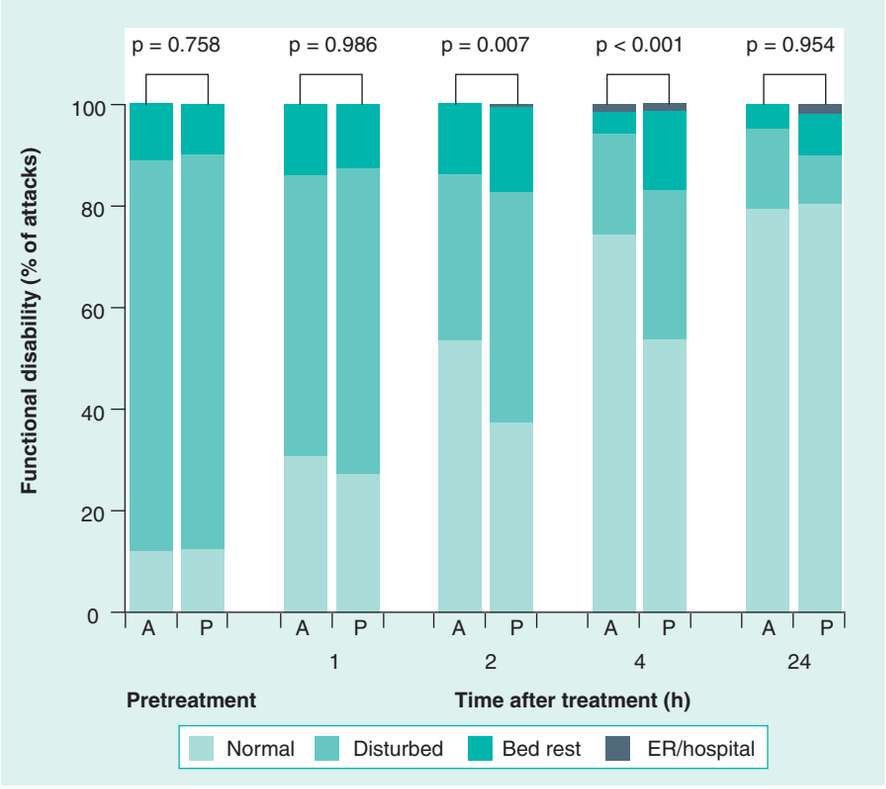

Figure 5. Effect of almotriptan 12.5 mg on functional disability at various time points after early treatment of migraine (<1 h after onset) in the Almotriptan Early Migraine Intervention Study (AEGIS).
Reproduced with permission from [40].

The Triptans: Efficacy in Migraine after Precocious Oriented Study

A French, prospective, crossover, open-label study (The Triptans: Efficacy in Migraine after Precocious Oriented [TEMPO]) also aimed to determine if early intervention with almotriptan (<1 h after pain onset) improved responses in patients usually using a triptan over 1 h after the onset of pain [41]. Patients (n = 193) who treated more than three migraine attacks were included (n = 147), and those who had treated at least two of the three attacks 'late' (>1 h after pain onset; n = 65) were instructed to treat their next three attacks early (<1 h), regardless of pain intensity. Early intervention was undertaken in 42 of these 65 patients. Early intervention significantly improved outcomes: 54% of patients taking almotriptan within 1 h of pain onset were pain-free at 2 h, compared with 38% of those taking almotriptan over 1 h after onset (p = 0.035). Being pain-free at 2 h was statistically associated with early intervention (odds ratio [OR]: 0.432), absence of allodynia (OR: 0.547) and mild pain intensity (OR: 0.604). Therefore, almotriptan given within 1 h of pain onset significantly improves outcomes, and almotriptan is more effective if given when the pain is mild, before it progresses to moderate-to-severe [41].

The Almotriptan Time Versus Intensity Migraine Study

The Almotriptan Time Versus Intensity Migraine Study (AIMS) was a prospective, multicenter, open-label, cluster-randomized study undertaken to determine whether early treatment with almotriptan (within 1 h of onset regardless of pain intensity; n = 757) was superior to 'standard' treatment (treatment when the pain intensity reached moderate-to-severe; n = 693) in terms of reducing the overall duration of migraine pain [10]. This study used the novel primary end point of total headache duration, defined as time from onset of migraine headache pain until complete resolution in the intention-to-treat population, for the first of two migraine attacks. As expected, median time-to-treatment was significantly shorter in those treating their migraine early, compared with those using 'standard' treatment (10 vs 90 min; p < 0.001). Early treatment also significantly reduced the overall duration of migraine pain compared with treatment that was given when the pain was moderate-to-severe (3.2 vs 5.5 h; p < 0.001). There were no significant differences between the groups in terms of being pain-free at 2 h (43 vs 39% for early vs standard treatment; p = 0.21), SPF (17 vs 15%; p = 0.31) or the use of rescue medication (36 vs 37%; p = 0.63). Almotriptan was well tolerated with a low incidence of adverse events in both the early and 'standard' treatment groups; dizziness and nausea were the only events that occurred in more than 1% of patients.

Owing to the unexpectedly large number of patients in the 'standard' treatment group who experienced early moderate-to-severe pain, making them eligible to take their medication early, *post hoc* subgroup analyses were undertaken to determine the relative contribution of pain intensity and timing of administration on almotriptan response. In addition to some patients treating moderate-to-severe pain within 1 h, some patients in the 'standard' treatment group also treated mild headache (n = 41;

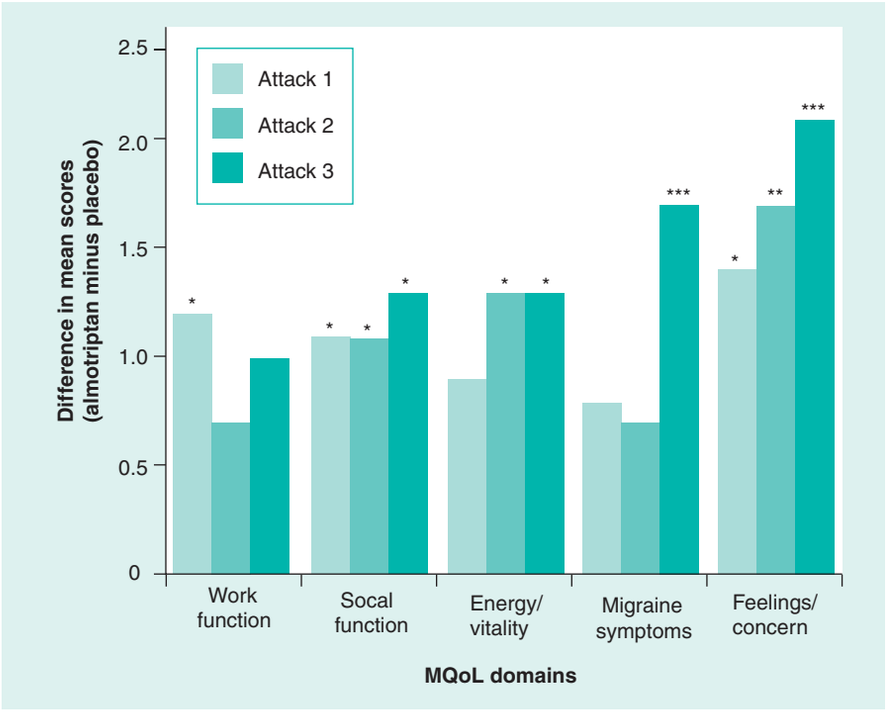

Figure 6. Improvement in health-related quality of life indicators associated with the early treatment of migraine (<1 h after onset) with almotriptan 12.5 mg in the Almotriptan Early Migraine Intervention Study (AEGIS).
*p < 0.05; **p < 0.01; ***p < 0.001.
MQoL: Migraine Quality of Life Questionnaire.
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they were not included in the subanalysis), and so the 'standard' group was redefined as treatment of moderate-to-severe pain no more than 1 h (n = 288) and over 1 h (n = 364). Some patients in the early treatment group did not treat their migraine early (n = 105), so the early group was redefined as 'early no more than 1 h' (n = 652). In this analysis treating mild or moderate pain was associated with a significantly shorter duration of headache compared with the treatment of severe pain (p < 0.001; Figure 7), and early treatment (≤1 h) significantly shortened the duration of headache compared with later treatment (>1 h; p < 0.001; Figure 8).

In the 'early no more than 1 h' group, 2-h pain-free rates were significantly reduced when mild or moderate pain was treated compared with severe pain (43 and 44% vs 31%; p < 0.05 for both vs severe), as were SPF rates (20 and 19% vs 9%; p < 0.005 for both), and the use of rescue medication (26 and 31% vs 51%; p < 0.001 for both). Similar patterns were seen in those treating moderate or severe pain for no more than 1 h and over 1 h: treatment of moderate pain compared with severe pain was associated with reduced 2-h pain-free rates (54 vs 18% in the ≤1 h group, p < 0.001; and 37 vs 23% in the >1 h group, p = 0.16), SPF rates (24 vs 8% in the ≤1 h group, p < 0.076; and 13 vs 7% in the >1 h group, p = 0.16) and the use of rescue medication (16 vs 31% in the ≤1 h group, p = 0.21; and 47 vs 62% in the >1 h group, p = 0.36). Furthermore, early treatment was associated with better outcomes than later treatment at the same pain intensity in those treating moderate or severe pain for no more than 1 h and over 1 h.

Evaluation of the prognostic variables demonstrated that treating severe pain predicted a longer total headache duration, compared with treating mild or moderate pain (risk ratio [RR]: 1.75; p<0.001) in those receiving early treatment. Headache intensity also predicted being pain-free at 2 h (RR: 1.73; p = 0.011), achieving SPF status (RR: 2.66; p = 0.004) and the use of rescue medication (RR: 2.45; p < 0.001). In the 'standard' treatment group, both pain intensity and time-to-treatment predicted a longer headache duration, with time to treatment a stronger predictor (RR: 2.86 vs 1.72; p < 0.001 for both); similar results were reported for the use of rescue medication (RR: 4.58; p < 0.001 vs 1.96; p = 0.005). Conversely, headache pain intensity rather than time to treatment was a better predictor of being pain-free at 2 h (RR: 2.80 vs 1.86; p ≤ 0.001 for both) and achieving sustained pain-free status (RR: 2.75 vs 1.81; p = 0.016 and 0.019, respectively).

Overall, the results of this subgroup analysis demonstrated that treating mild or moderate pain with almotriptan was associated with significantly shorter total headache duration than treating severe pain. Initial pain intensity was an important predictor for achieving pain-free status at 2 h and SPF status. Importantly, early treatment with almotriptan (≤1 h) was associated with significantly shorter total headache duration compared with later treatment (>1 h) at the same pain intensity, with time-to-treatment being an important predictor of headache duration and the need for rescue medication [10].

The 'Act When Mild' study

The 'Act When Mild' (AwM) study was a randomized, double-blind, placebo-controlled, multicenter study undertaken to determine the response to almotriptan in patients who took their medication early in the course of an attack when the pain was mild and to compare this with the response in patients who took almotriptan when the pain has become moderate or severe [11]. Patients were randomized to receive almotriptan 12.5 mg or placebo when pain was mild and within 1 h of onset, or almotriptan 12.5 mg or placebo when the pain was moderate-to-severe. Patients who did not take their study medication as defined in the protocol were reassigned prior to unblinding for re-analysis of the primary end point, which was pain-free status at 2 h. Significantly more patients were pain-free at 2 h when treating their migraine with almotriptan early when the pain was still mild (AwM group) compared with treating moderate-to-severe pain (p < 0.02). Significantly more patients in the AwM group also achieved SPF status (p < 0.026; Figure 9), and this

was reflected in the difference in recurrence rates between the two groups (6% in the early/mild group and 24% in the moderate-to-severe group; p = 0.0124). The mean duration of headache was also significantly shorter in the AwM group compared with those treating moderate-to-severe pain (p = 0.0005; Figure 9), and this was associated with a significantly lower impact on the patients' ability to resume daily activities 48 h after dosing (0 vs 2 h, respectively; p = 0.0015).

Adverse effects were reported in less than 5% of patients in all four groups, with no serious events documented. There was no indication of any differences in the nature or incidence of adverse events when treating mild/early migraine compared with moderate-to-severe migraine.

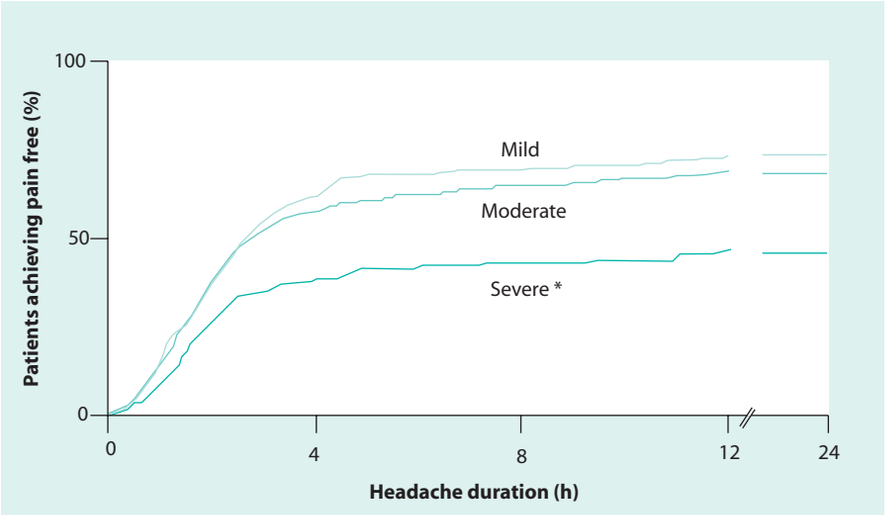

Figure 7. Effect of migraine pain intensity at time of treatment in patients taking almotriptan 12.5 mg at the earliest onset of pain, and within an hour of onset in the AXERT 12.5 mg Time Versus Intensity Migraine Study (AIMS) (n = 652).
The numerator does not include patients taking rescue medication.
*p < 0.001 severe vs mild or moderate.
Reproduced with permission from [10].

The AwM study employed a questionnaire to assess the presence of allodynia at baseline, 2 h after treatment and its effect on treatment outcomes [11,42]. The investigators found that allodynia at baseline did not predict a poor outcome when almotriptan was taken early after migraine onset when the pain was mild, and that baseline headache intensity was the key predictor of clinical outcome [11]. However, delaying treatment until the pain was moderate-to-severe resulted in significantly poorer outcomes in general, and particularly in those with allodynia (p < 0.031) [42].

The results of the AwM study demonstrated that almotriptan 12.5 mg taken early after migraine onset when the pain was mild, rather than waiting until pain became moderate-to-severe, significantly improved patient outcomes, and this improved efficacy is unaffected by the presence of allodynia. The results of this study also confirm the high efficacy and placebo-like tolerability profile of almotriptan that was reported in earlier studies.

Cutaneous allodynia

Some believe that early treatment with triptans may prevent central sensitization and that triptans may be less effective if initiated after the onset of cutaneous allodynia [14,15]. A pilot study was undertaken to evaluate the presence of cutaneous allodynia (as determined by typical symptoms) and its influence on the efficacy of almotriptan plus the NSAID aceclofenac [43]. The results were assessed in relation to the severity of migraine headache at the time of treatment. Allodynia was reported in 34% of attacks and was proportional to headache severity. Although all efficacy measures were numerically worse in allodynic attacks than in nonallodynic attacks, the differences did not reach statistical significance. Indeed, it was headache intensity at the time of treatment that significantly influenced most outcome measures. The authors concluded that there is a complex relationship between headache intensity, allodynia and treatment outcome and suggested that headache severity may drive allodynia and may be a better criterion for optimizing migraine treatment [43]. Similar results and conclusions were reported for almotriptan in the AwM study (see details in previous section) [11,42], and have also been documented for rizatriptan [44].

Choosing the appropriate triptan

As a number of triptans are now available, each demonstrating different efficacy and tolerability profiles [6,7], how can physicians select the most appropriate drug for their patient? Several attempts have been made to aid this process.

The System of Objectified Judgement Analysis (SOJA) is a model for rational drug selection that encompasses all relevant aspects for a specific class of drugs and it was designed to aid formulary decision-making [45]. A panel of experts identify selection criteria and assign a relative weighting based upon their relative importance. Such an analysis was performed for the triptans and the selection criteria were: approved indications, available formulations, variability in bioavailability, drug interactions, efficacy, tolerability, direct acquisition cost and published randomized, double-blind, controlled, comparative trial evidence [46]. Almotriptan 12.5 mg achieved the highest SOJA score (810) suggesting that it is most suitable for formulary inclusion, followed by rizatriptan (804). Almotriptan was the drug of choice, despite the fact that at the time the analysis was undertaken it had one of the lowest scores for published randomized, double-blind, controlled, comparative trial evidence (63 compared with 88 for rizatriptan and 105 for sumatriptan 100 mg).

Based on evidence from a meta-analysis of controlled clinical trials [6], TRIPSTAR, a multi-attribute decision model, was used to match the attributes of oral triptans to particular types of patient to determine whether measurable clinically relevant

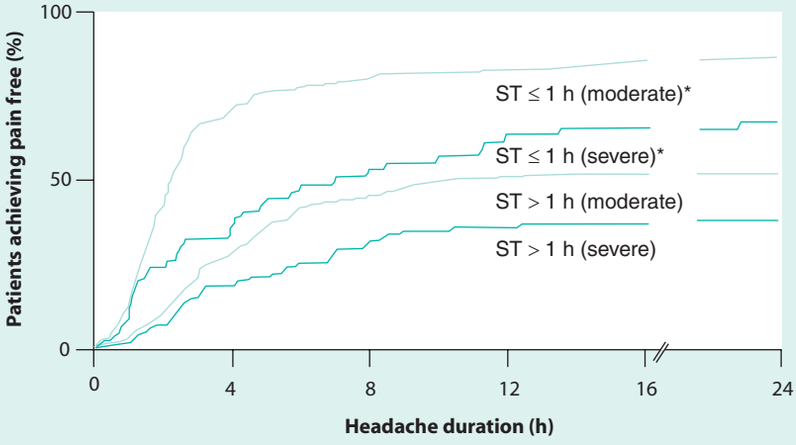

Figure 8. Effect of time-to-treatment in patients taking almotriptan 12.5 mg when pain reached moderate or severe intensity (ST) in less than 1 h and more than 1 h in the AXERT 12.5 mg Time Versus Intensity Migraine Study (AIMS) study.
*p < 0.001 vs ST > 1 h
Reproduced with permission from [10].

differences were apparent [47]. Almotriptan 12.5 mg was consistently ranked among the top three triptans, that is, closest to the ideal triptan, in six separate analyses, each of which were undertaken using placebo-corrected data and absolute data and allowed for different preferences for triptan-naive and triptan-experienced patients (Figure 10). In light of the fact that the meta-analysis included early controlled studies with almotriptan [6,7], one might expect a reanalysis that includes recent data demonstrating the improved efficacy of almotriptan 12.5 mg given early during a migraine attack and when the pain is mild, to highlight its position as one of the drugs of choice for acute migraine treatment [10,11,39].

Challenges of early treatment

Although the clinical evidence demonstrates the benefits of almotriptan 12.5 mg given early, when pain is still mild, in patients with acute migraine headache, there are a number of physician and patient barriers that need to be overcome in order to ensure optimal clinical outcomes.

Physician-related challenges include correctly diagnosing migraine (~50% of patients in the USA are misdiagnosed with sinus and tension-type headache [48]), which adversely impacts their prescribing habits [49]. Similarly, in a recent survey evaluation involving European physicians, the overall results in terms of diagnosis and management of headache in primary care were poor. This was particularly the case for patients with chronic migraine, medication-abuse headache and tension-type headache, and the authors concluded that continuing medical education and referral to specialist care needed to be improved to rectify the situation [50]. Physicians employ a number of paradigms to treat migraine. The traditional step-care approach involves starting with nonspecific analgesics and progressing sequentially and hierarchically through options until the optimal solution is reached, but dissatisfaction on the part of the patient can lead to them seeking their own solution, and so never reaching the triptan stage in this process [49]. A stratified-care approach avoids the trial-and-error period of stepped care, and individualizes treatment to the patient's symptoms and needs, promoting a good relationship between physician and patient (since the patient's expectations of therapy are targeted and, if necessary, managed) and, as a result, it is more likely to increase the patient's adherence to treatment [49].

Patient-related challenges include their confidence in their physician and their perceptions of migraine and its treatment [13]. There are many reasons for patients delaying migraine treatment, including waiting to see if a headache develops into a migraine [51], although experienced migraneurs can usually identify a migraine at onset [52], and waiting to see if migraine pain worsens [51]. Fear of side effects [12] and risk of medication overuse [49] are also patient-related barriers. Good communication between patient and physician can address some of these concerns. Importantly, almotriptan 12.5 mg is very well tolerated and communicating this to patients can help alleviate the fear of adverse effects [22]. It has also been shown to significantly reduce recurrences and the need for rescue medication, thus reducing the risk of medication overuse [10,11,24,34,35,39].

Cost–effectiveness

A number of pharmacoeconomic analyses of the triptans have been undertaken, and specifically with almotriptan. Brief details are given regarding the studies examining the direct costs of triptans using the patient-orientated end points SPF and SNAE. All analyses used efficacy and safety data from the meta-analysis of 52 controlled clinical trials involving the triptans [6].

A US analysis that determined the cost of 100 patients achieving SPF and SNAE (2004 US$ prices) reported that almotriptan 12.5 mg was the most cost-effective triptan for both of these end points [53]. Another US analysis calculated the cost per attack when SNAE was achieved (2004 US$ prices) for almotriptan 12.5 mg and sumatriptan 50 and 100 mg [54]. Again this analysis showed that almotriptan was the most cost-effective agent (US$82, 133 and 138 per SNAE, respectively). Further analysis exploring the impact of other healthcare costs, doses required, variability in cost and using different outcome results for those used in the original analysis confirmed that almotriptan was the most cost-effective agent.

A similar analysis was undertaken in Italy [55]. They calculated that 386 patients would need to be treated with almotriptan 12.5 mg for 100 patients to achieve SPF, and 393 patients for 100 to achieve SNAE. The next most cost-effective triptan was rizatriptan 10 mg, which required 395 and 457 to be treated for 100 patients to achieve SPF and SNAE, respectively.

These analyses did not consider health-related quality of life and migraine-associated disability and productivity. The efficacy and tolerability of triptans result in improvements to the patient's quality of life and daily functioning, increasing their productivity and reducing disability-associated costs [56]. This was recently clearly demonstrated in Spain using a decision-tree model based upon a randomized, double-blind, clinical trial comparing almotriptan with ergotamine plus caffeine [57]. This pharmacoeconomic analysis was performed from a societal perspective and included indirect costs resulting from absenteeism and loss of productivity. The impact on quality of life was also investigated by assigning utilities for migraine patients that are available in the published literature. In this analysis almotriptan was more cost effective than the combination of ergotamine plus caffeine and it was the dominant option in terms of clinical efficacy and of being more economical from a societal perspective [57]. In addition, improved outcomes when a patient treats a migraine attack early when the pain is still mild, should increase the overall response. This would be expected to further improve the cost–effectiveness of almotriptan, not only owing to increased efficacy, but also due to the improvements in quality of life and daily functioning, thus reducing the number of lost work days and increasing productivity.

Conclusion

The data presented clearly demonstrate that the already established benefits of almotriptan 12.5 mg are significantly increased when it is administered within 1 h of headache onset and particularly when migraine pain is mild. Improved outcomes were also demonstrated for the early treatment of migraine headache of moderate and severe intensity. Indeed, based in part on the results from the AwM study with almotriptan 12.5 mg, the Acute Migraine Treatment Practice parameter of the American Academy of Neurology has acknowledged the benefits of early treatment with triptans. These agents are now recommended since they improve outcomes and are well tolerated, and they reduce the need for rescue medication and the potential to overuse medication [49].

In particular, almotriptan has been shown to be very effective and well tolerated when administered early, and it is a cost-effective option for improving patient-orientated outcomes, including quality of life and improved productivity. These attributes indicate that almotriptan may be a useful treatment option and may help to overcome some of the physician- and patient-related barriers to the early treatment of migraine. The current best evidence suggests that if this can be achieved then we might start impacting the significant burden that this common disorder places on the patient, healthcare systems and society.

Expert commentary & five-year view

The magnitude of the burden that migraine places on the individual, families and friends, healthcare systems and society in general is enormous. This is not only because of the 'individual debilitation' associated with migraine attacks *per se*, including lost work time/productivity, but also because of the high prevalence of the disease. The problem is compounded by the view of some patients and healthcare professionals that, for example, migraine is not a serious disease, 'not much can be done about it in any case', it can be treated adequately with over-the-counter medications and it does not require medical attention. The net effect of such conceptions/misconceptions is that migraine remains a disease that is poorly understood, poorly diagnosed and poorly treated; hence the huge burden it places on society.

This is now becoming a focus for many experts working in the migraine field to address questions such as:

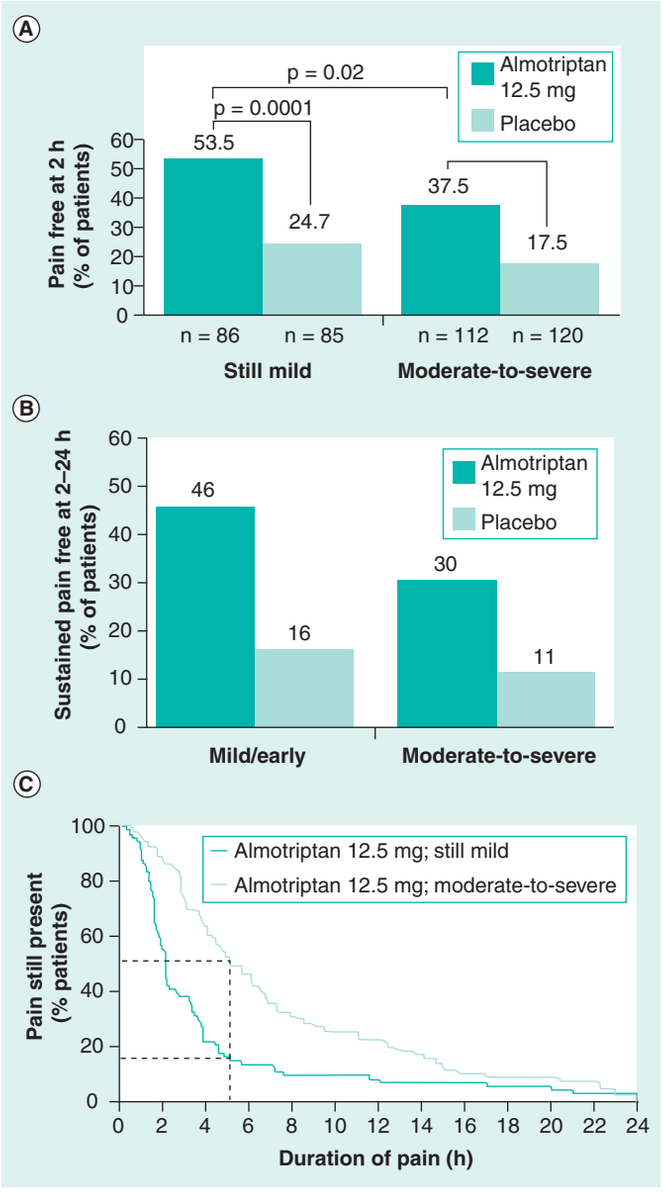

Figure 9. Efficacy results in the 'Act when Mild' study in patients treating migraine early, within 1 h of onset, when the pain is mild or when the pain is moderate-to-severe.
(A) Pain-free at 2 h. **(B)** Sustained pain-free (2–24 h).
(C) Duration of migraine.
Reproduced with permission from [11].

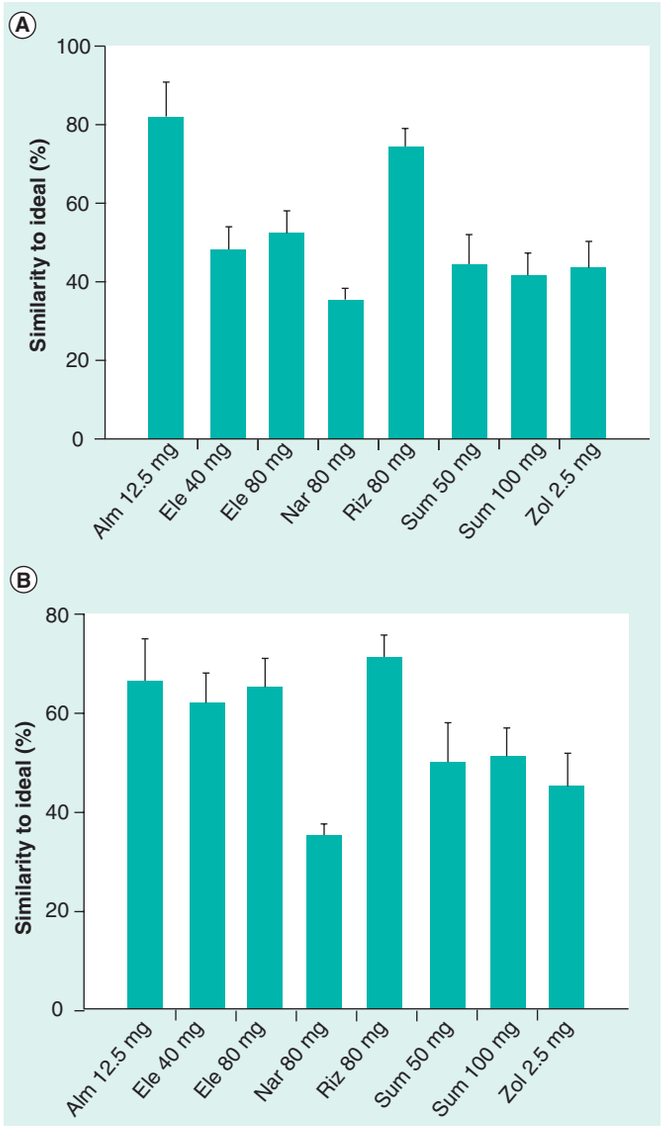

Figure 10. Similarity to the ideal triptan for a given patient using the TRIPSTAR multiattribute decision model weighted according to physician ratings. (A) Absolute data; **(B)** placebo-corrected data.
Alm: Almotriptan; Ele: Eletriptan; Nar: Naratriptan; Riz: Rizatriptan; Sum: Sumatriptan; Zol: Zolmitriptan.
Reproduced with permission from [47].

- Why don't patients seek professional advice when disease worsens?
- How do we improve the patient–physician relationship?
- What are the barriers to successful diagnosis?
- When do physicians need to request specialist help?
- What is the best treatment for the patient: prophylaxis, acute pain relief with simple analgesics, acute pain relief with triptans?

We now have better therapeutic options than ever to treat patients with migraine. This includes a variety of drug classes for disease prevention in patients with chronic disease and a clear understanding of the benefits of early intervention in patients suffering an acute migraine attack. Over the next 5 years if we can align these therapeutic approaches with improved diagnosis, better communication between the patient and the physician, increased clinic attendance by patients and referral to specialist help when required, then we believe that we can reduce some of the significant burden associated with migraine headache.

Financial & competing interests disclosure

Fabio Antonaci has been a guest lecturer at several Almirall Annual Migraine Meetings. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Clinical trials over the last 10 years have confirmed the efficacy and placebo-like tolerability of almotriptan in the treatment of acute migraine headache.
- Almotriptan has a rapid onset of action and patients achieve pain relief and become pain-free as early as 30 min after administration.
- Almotriptan is significantly superior to placebo in improving the composite end points of 'sustained pain-free' and 'sustained pain-free with no adverse effects', which include treatment attributes important to patients.
- Pivotal randomized controlled trials have shown that almotriptan 12.5 mg taken early after migraine onset when the pain was mild, rather than waiting until pain became moderate-to-severe, significantly improves patient outcomes.
- Treating moderate-to-severe pain early with almotriptan was significantly superior to placebo in terms of pain relief.
- This improved efficacy associated with almotriptan administered early, when the pain was still mild, was not affected by the presence of allodynia.
- The System of Objectified Judgement Analysis (SOJA) is a model for rational drug selection that encompasses all relevant aspects for a specific class of drugs and it was designed to aid formulary decision-making. Almotriptan 12.5 mg achieved the highest SOJA score suggesting that it is most suitable for formulary inclusion, followed by rizatriptan.
- In economic analyses performed to date, almotriptan has been shown to be amongst the most cost-effective triptans.

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TUTORIAL

Guidelines for the organization of headache education in Europe: the headache school II

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Abstract In order to promote education on headache disorders, European Headache Federation (EHF) in conjunction with National Headache Societies organizes educational courses meeting uniform standards according to previous published guidelines. Based on six headache summer schools' experience, an EHF subcommittee has reviewed these guidelines, and here the revised version is presented. The goals remain the same: quality courses that will attract physicians and neurologists seeking to increase their knowledge, skills, and understanding in the area of primary and secondary headache. Detailed guidelines, a day-to-day program, and a multiple-choice test battery have now been outlined. It is recommended to include practical sessions with patient interviews and hands-on demonstrations of non-pharmacological treatment strategies. For countries that want a 'low cost' education program, a Video School program of a similar scientific standard has been developed. To be certified for CME credits, patronage, and financial support from EHF, it is highly recommended to adhere to the suggested teaching strategies. We hereby aim to promote and professionalize the education in headache disorders and endorse the educational courses meeting uniform standards of excellence.

Keywords Education · Europe · Headache

Introduction

According to its mission statement, one of the aims of the European Headache Federation (EHF) is to "educate Europe" about headache [1]. In line with this goal, EHF published in 2005 guidelines addressing key issues for organizers of headache schools under the patronage of EHF [2]. Since then, six headache schools have been organized (http://www.ehf-org.org) in Italy, Greece, Denmark, Azerbaijan, France, and Spain. A total number of 345 registrants have participated and hereof 89% were MD's. The format, quality, and evaluations have continuously been evaluated by the participants and an EHF subcommittee, and on this basis these guidelines have been revised. The new version is presented here. New rules not only deal with financial support mainly but also with the applications from National Headache Societies.

As in the previous paper [2], a sample course outline, developed in accordance with the systematic guidelines presented in this paper, is given below, together with a check list for applicants (see Appendices 1, 2, and 3).

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Teaching course format

Target of the guidelines

These guidelines are aimed at institutions, such as National Neurological and/or Headache Societies, European Neurological Societies or allied scientific organizations that are planning to organize headache teaching courses at postgraduate level.

Aim of the course

The aim of the course is to enable participants to gain knowledge, skills, and understanding in the area of primary and secondary headache as well as the organization of headache care, and thereby contribute to their personal and professional development. By the end of the course, they should have enhanced their clinical skills, including their capacity to interact appropriately with affected individuals. Ideally, this should translate into an enhanced quality of life for headache sufferers. The key aim is that the knowledge gained from the course can be applied in the participants' various professional fields. The National Society/Research Group hosting the course will apply to the appropriate authorities, national or European, for continuous medical education (CME) credits. In this way, the participants will be attending a certified course that can be a contribution to the university career. The target audience may include general practitioners with special interest in headache, general neurologists, clinical pharmacologists, and internal medicine specialists; the course brochure specifying which of these is aimed at and planned accordingly. The teaching course must be specifically designed to help participants to:

- recognize the various clinical presentations of headache;
- become familiar with the "red flags" and "comfort signs" approach to diagnosing secondary headaches;
- understand the latest concepts in headache pathophysiology;
- develop treatment plans for helping patients with all aspects of their headache treatment needs;
- formulate a headache management "toolbox" for patients, incorporating acute and preventive treatment approaches;
- devise strategies in order to help patients understand headache treatment tactics and improve patient compliance with therapeutic plans [3];
- provide strategies and plans for organization of national headache care [4].

Topics

Each day of the course, which should cover both primary and secondary headaches, must incorporate both theory and practical teaching. The organizers should ensure that any slides used are kept as concise as possible, given that it takes at least 40–60 s to explain and understand a slide. Speakers must submit their slides in plenty of time so that they can be printed or downloaded on an electronic media (USB-stick, CD-ROM or website) and available for distribution, on a daily basis, during the course. Patient demonstrations and interviews by the participants in small groups (6–8 per group) in rotation are the best medium for practical training under qualified supervision of the lectures. Alternatively video recordings are valuable for presenting illustrated case reports on both simple and complex cases and for making sure that the participants retain the information given. Ten-minutes interview or video plus 10–15-min discussion time are usually enough to become familiar with a clinical history. At least two patient-demonstrations, two videos or hands-on demonstrations of non-pharmacological treatment strategies per day should be included in the program.

Venue

The course should preferably be organized in a hospital/university setting, providing optimal facilities for demonstrations of patients, non-pharmacological treatment strategies or research laboratories.

Duration of the course

The ideal/minimum duration of a course is 3 days with at least 6 h/day theoretical teaching. Concise 1-day courses can be organized under the supervision, or with the advice of the EHF, on condition that the recommended ratio of practical/theoretical teaching is respected. Due to the necessity of a minimal set of education (especially for general practitioner) we are currently working on a 6-h format Headache School that is the minimum for obtaining European and national CME credits.

Participants and structure of lectures

Overcrowded courses prevent the participants from interacting with the lecturers and clearly lower the general level of attention. Around 50 participants should be admitted, ideally divided into two or more parallel sections. The attention of the participants is negatively correlated with the length of the lecture. On the basis of

prevailing experience, duration of 20–25 min (+5 min for questions) is recommended. The course program should schedule 7–8 teaching hours per day (approximately 15 lectures/case reports). A key element in courses of this kind is the practical demonstrations, patient interviews, panel discussion or discussion groups, which should never be missing from the program. Participants have to be neurologists, general physicians, or psychiatrists or ophthalmologist or ENT (either registrants or young fellows) with a general knowledge on headache field or which to get one. Participants have to be either beginners or with a general knowledge on headache field.

Teaching staff

The course should provide participants with an opportunity to share in the experience of international scientists and to exchange opinions and ideas. A 3-day course should have a teaching staff of 3–5 foreign lecturers (local finances permitting), who should each be given the opportunity to give at least two lectures and demonstrate patient interviews. The local organizers will give the remaining lectures and organize the patient demonstrations and the practical treatment sessions. The discussion at the end of each lecture or at the end of a session gives all the participants an opportunity to express their ideas, considerations, second thoughts, etc. Therefore, each session should have at least two chairmen, whose role is to raise controversial issues and questions, requesting the speaker to express his own personal opinion, or international opinion, on certain topics.

Official language

The official language of the course should possibly be English; in certain situations, national languages can be used, provided that students or doctors are offered simultaneous translation.

Teaching material

Slide handouts and relevant scientific publications including state of the art reviews for each major topic selected by the lecturer as well the EHF-guidelines for the management of common headache disorders in general practice [3] should be available at the beginning of the course, either in paper or electronic format. The course material should also include brief curriculum vitae of each lecturer. The EHF secretariat may eventually help the local congress organizer in the assembling of the teaching material and e-mail that to the local secretariat.

Evaluation test and diploma

A standardized multiple choice questionnaire should be filled in by each participant at the beginning and at the end of the course. The evaluation test should include 2–3 questions relating to each lecture. The test results will be mailed to the participants after the course if requested. The EHF may provide an evaluation questionnaire if requested by the organizers. In order to gain CME credits, the participant should attend 80% of the scheduled activity. CME should be based on European authorities mainly and if the organizers suggest to national as well. All participants will receive a personal diploma, where the name, the objective, and the CME credits are displayed. The participants will also be asked to give their evaluation of the speakers and lecturers,

Miscellaneous

The course format should be included in the preliminary and final program brochure. In order to be formally approved by the EHF, the course format should be mailed to the president of the European Headache Federation who will distribute the application to the federation's board members for approval. The EHF may offer financial support covering registration and accommodation to 2–3 participants from each country included in the developing countries list [5] with limited local funding after a written recommendation from their national EHF-representative.

The local organizing committee and the course chairman are fully responsible for promoting and marketing the course locally. EHF distributes the program via the website and mails directly to the national representatives at least 2–3 months in advance. The EHF congress secretariat may help the local congress company with logistical organization if requested.

The EHF can, upon request, provide the following material:

IHS classification slide kit;
evaluation test;
standard 3-day program (see Appendix 2);
currently available teaching materials (booklets, manuscripts, guidelines, patient brochures, etc.);
diploma.

Applications

1. A complete program and a preliminary budget for European Schools should be submitted and approved by EHF board at least 6 months before announcement. After approval, the EHF logo and the EHF patronage should appear clearly on the program.

2. The national EHF representative should add a letter of recommendation of each candidate for the EHF grant together with the application.
3. The organizing national headache society (or societies) is fully responsible for the finances and EHF only secure the academic standard and support with the present grants according to the rules mentioned above (for the EHF responsibilities please see Appendix 3).

Headache Video School

Besides the frontal headache education described in the present document, the previous version of the guidelines for organizing a headache school needs to be updated on the basis of new media education technologies. The EHF has recently collected all the lectures presented at the European Headache School held in Mallorca on 12–14 March 2009 in a DVD. Such material is the core for a Video School available on request from countries that want a 'low cost' education program to be held. Therefore, a video school format has been constructed providing approximately 3-h video teaching (with a local chairman) and 1-h online discussion with an international chairman two times a day for 3 days. The advantage of such school for the applying country are: low cost for local organizers (no cost for speakers), excellence of the faculty, participation of a larger number of local doctors than those who are able to attend a school abroad (i.e. 2–3 per country on EHF finances). A fast-band internet connection (ADSL) should be checked well in advance for online discussion at the end of each session.

The request of such school material to the EHF is free until October 2010. After that date, due to the necessity of updating/replacing some lectures, a small royalty needs to be payed to the EHF. The request for the European Headache Video school has to be directed to the EHF president. Due to the necessity of a minimal set of education (especially for general practitioner), we are currently working on a 6-h format Headache School that is the minimum for obtaining European and national CME credit (see above). Information for frontal and video headache school is constantly updated at EHF web site [6].

Concluding remarks

In order to promote education on the very prevalent headache disorders, EHF organizes and endorses educational courses meeting uniform standards of excellence. Based on recent summer schools' valuable experience, the guidelines have been revised and updated. A detailed review and validation process is planned after five additional headache schools. The primary goals to increase knowledge, skills, and understanding of headache disorders are emphasized. Likewise, organization of headache care, education, and research are important key elements to be implemented in future summer schools.

Conflict of interest None.

Appendix 1: Checklist of European Headache Federation requirements for the organization of a teaching course on headache

1. Title of the teaching course:
2. Date:
3. City:
4. Chairman of the scientific committee:
5. Institution:
6. E-mail/fax:
7. Congress venue:
8. Number of participants:
9. Parallel sections:
10. Number of foreign lecturers:
11. Duration of the course:
12. Duration of the lectures:
13. Daily practical/theoretical teaching:
14. Telematic media:
15. Application for CME-points:
16. Multiple-choice evaluation test:
17. Handout material requested:
18. Official language:
19. Guidelines provided with course material:
20. Preliminary program submitted:
21. Diploma:
22. Budget:
23. Notes:

Appendix 2: Sample format of a 3-day headache course:

Local organization for the study of headache in conjunction with European Headache Federation presents:

Title of the course
International school on headache and related disorders
Venue, city
Day 1–3 month, year

Day 1
08.30–10.30 Introduction to headaches
08.30 Welcome and test
08.45 Classification of Headache
09.00 Epidemiology and burden of headache
09.30 Taking the headache history with patient demonstrations (group sessions)

10.30–11.00 Coffee break
11.00–13.00 Migraine I
11.00 Classification of migraine
11.30 Pathophysiology of migraine
12.00 Clinical picture of migraine
12.30 Complications of migraine
13.00 Lunch
14.30–16.30 Migraine II
14.30 Patient or video-case demonstrations
15.30–16.00 Comorbidities of migraine
15.30–16.00 Acute drug treatment
16.30–17.00 Coffee break
17.00–18.00 Prophylactic drug treatment
Day 2
08.30–10.30 Tension-type headache (TTH)
08.30 Classification and clinical picture of TTH
09.00 Epidemiology and burden of TTH
09.30 Pathogenesis of TTH
10.00 Comorbidities of TTH
10.30–11.00 Coffee break
11.00–13.00 Tension-type headache II
11.00 Pharmacological treatment of TTH
11.30 Non-pharmacological treatment of TTH
12.00 Temporomandibular dysfunction and headache
12.30 Medication-overuse headache
13.00–14.00 Lunch
14.30–16.30 Various I
14.30 Patient or video-case demonstrations
15.00 Cervicogenic and other secondary headaches
15.30 Headache in the emergency department
16.00–16.30 Coffee break
16.30–18.00 Various II
16.30 Other primary headaches
17.00 Cranial neuralgias
17.30 Which examinations in headache
Day 3
8.30–10.30 Trigeminal autonomic cephalalgias (TACs)
08.30 Epidemiology and classification of TACs
09.00 Pathogenesis of TACs
09.30 Clinical picture of TACs with patient or video-case demonstration
10.00 Pharmacological treatment of TACs
10.30–11.00 Coffee break
11.00–13.00 TACS II and other
11.00 Paroxysmal hemicrania and other TAC's: clinical picture, differential diagnosis, and treatment
11.30 Post-traumatic headache, high and low pressure headaches in relation to other secondary headaches: clinical picture, differential diagnosis, and treatment
12.30–13.30 Lunch
14.00–16.30 Various III
14.00 Headache in the elderly: diagnosis and treatment
14.30 Headache in children: diagnosis and treatment
15.00 Headache and reproductive life
15.30–16.30 Test and evaluation

Appendix 3: EHF responsibilities

- Complete list of headache schools participants, programs, tests, diplomas, and applications for CME grants will be kept in EHF available for future organizers.
- EHF intends to sponsor the registration and accommodation of a maximum of ten European doctors, and a maximum of 2–3 doctors from each country.
- A headache school subcommittee, consisting of three members from the EHF executive committee (including the treasurer), evaluates the EHF-grant applications independently of the organizers.
- The EHF grant is maximum 600 Euros per person and is restricted to cover registration, and accommodation up to three nights during the Headache School. No economical support is provided for transportation expenses.
- The EHF is not responsible for the administrative issues connected with the organization of the Headache school. The economical support is granted, provided the criteria are satisfied.
- The EHF grant should only be reimbursed from EHF after the Headache School and after the participation has been confirmed by the organizers. The reimbursement should be directed from EHF to the organizers, not to the individuals.
- A complete review of the summer schools, the test results, and evaluations should be kept in EHF available for future organizers, and a summary should be available on the EHF website [6] and in the EHF news [6].

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Therapy-resistant cluster headache in childhood: Case report and literature review

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Therapy-resistant cluster headache in childhood: Case report and literature review

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Abstract

The mean age of onset of cluster headache (CH) is in the late third decade. Only few cases of childhood-onset (< 14 years) CH have been reported in the literature. We report the case of an 11-year-old boy who suffered from sudden attacks of shock-like, intense pain, localized in the right orbital region, with associated photophobia, phonophobia, conjunctival injection, lacrimation, nasal congestion, rhinorrhoea and psychomotor agitation. The episodes lasted 60–180 min, and the headache frequency was one to three per day. Physical and neurological examinations, magnetic resonance imaging and blood examinations were normal. The first bout lasted 8 months. Attacks were resistant to every symptomatic and partially to prophylactic treatment that has been tried. The second bout lasted approximately 2 months.

Keywords

Cluster headache, childhood, drug resistance

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Introduction

Cluster headache (CH) is one of the most severe types of headache, characterized by periods of recurrent attacks of sudden and intense pain, localized in the orbital or temporal region, and associated with ipsilateral autonomic symptoms and signs (1).

Epidemiologically, CH is a relatively rare disease, affecting < 1% (i.e. 0.39%) (2) of the population, with a clear male preponderance (84%) (3), and the mean age of onset is 28–30 years (range 7–83 years) (4).

There are relatively few reports on the prevalence and clinical features in CH in children and adolescents, since only few population studies have also considered the paediatric population (5–8). To our knowledge, at paediatric age (0–18 years), CH has been considered to have the same clinical features as in adulthood. CH in this age range is rare, the estimated prevalence being 0.09–0.1% of the population. According to different studies (4–6,8,9), the sex ratio is approximately the same (M : F ~3.2 : 1), but with a wide variation of range (1 : 1–6 : 1). Onset may be as soon as 3 years, but there is a relatively low number of cases with onset < 10 years old. A suspected case in a 1-year-old infant has also been described (10).

Case report

An 11-year-old boy was referred to our department due to recurrent severe, short-lasting and unilateral side-locked headache.

There were no close relatives with CH. Delivery, psychomotor and language development were normal. Since the age of 2.5 years he had suffered from episodes of deviation of the right eye and esotropia, for which he was initially treated with occlusion therapy. At 9 years, medial rectus and inferior oblique muscles in the right eye (the present symptomatic side) were operated upon.

Since 8 years of age, he had presented mild band-like headache episodes (~2/year), without associated

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Data source	history / parental report					observation + headache diary							
Time	Sept '06	Oct '06	Nov '06	Dec '06	Jan '07	Feb '07	Mar '07	Apr '07	May '07	Jun '07	Jul '07	Aug '07	Sept '07
7				xxx	x								
8													
9			xxxxxx										
10			xxxx	xxxxx									
11			xx	xx	xxx								
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1													
2			x		xx								
3					xxxxx								
4					x								
5													
6													
Duration 1st attack	/	1 h	1-3 h	1-3 h	1-3 h	50 min	55 min	55 min– STOP	/	/	/	/	/
Duration 2nd attack	/	1 h	1-3 h	1-3 h	1-3 h	50 min	55 min	55 – 40 min	40 min – STOP	/	/	/	/

Figure 1. Temporal pattern of headache attacks September 2006 to May 2007. x, single episode retrospectively reported by parents; grey box, headache attack occurrence, from headache diary.

symptoms, lasting about 0.5 h; headaches were ketoprofen (80 mg)-responsive according to his parents.

At the age of 10.5 years, he started complaining of 30 min long attacks of sudden pain, described as sharp or shock-like, localized in the right orbital region. The intensity was severe, and pain was associated with photophobia, phonophobia, conjunctival injection, lacrimation, nasal congestion, rhinorrhoea and psychomotor agitation. The attacks had an initial daily fluctuating frequency (1–3/day), recurring at fixed hours of the day, and lasting in the full blown state for 60–180 min. The attack frequency has been reconstructed retrospectively collecting medical history on the basis of written notes by the parents during the months preceding our first observation.

In the clinical history reconstruction, occurrence of episodes was different from that subsequently observed, probably due to incorrect reporting by parents or to modifications in the timing of headaches, since sometimes three episodes per day were reported. Anyway, a sort of 'grouping' (or clustering) in specific hours of the day can be estimated.

Later on, using a headache diary, the daily frequency was two time-locked attacks, of 50–55 min duration. Attacks remained time-locked even during the beginning of daylight saving time in our country (Fig. 1). During the symptomatic period the patient was given different symptomatic and prophylactic pharmacological treatments and was under direct observation (as in-patient and out-patient) for 2 months, during the first cluster period. When admitted, several episodes were directly seen by different doctors, confirming the clinical diagnosis. Moreover, video documentation was obtained, but the video does not clearly show unilateral signs, because the boy was weeping/crying from pain.

The first bout lasted 8 months, with a progressive reduction in duration/frequency (Fig. 2)

Neurological examination was normal (weight 40 kg, height 156 cm). Blood examinations, including coagulation and inflammatory variables, showed no significant alterations. Brain computed tomography, magnetic resonance imaging (MRI) and angio-MRI were normal, except for mild asymmetry of the ventricular system (right>left). Electroencephalography showed slow posterior potentials during hyperpnoea (within normal range). Cardiological examination, ECG, echocardiography, transcranial Doppler, and echo-Doppler of the supra-aortic vessels were all

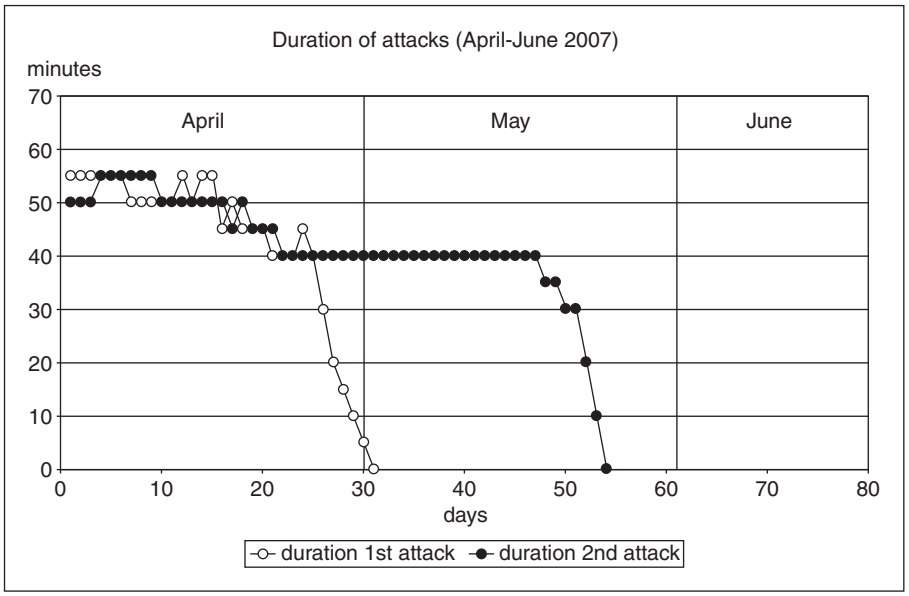

Figure 2. Temporal pattern of duration of headache attacks.

normal. Ophthalmological examination showed normal fundus, absence of binocular vision, with alternate eye suppression, and hypermetropic astigmatism.

Three months after the onset of headache, while tapering off the corticosteroid therapy started prior to our observation, he presented a cutaneous macular eruption resembling mastocytosis. A cutaneous biopsy instead showed the presence of trichostasis spinulosa.

The second bout was at first characterized by episodes of 'sense of heat' in the same area of the head as the previous bout. Pain was absent, but mild and inconsistent autonomic unilateral signs (i.e. lacrimation) were noticed. The duration was between 2 and 6 h. These episodes were not daily for a while, progressively showing a daily frequency. After 1 month he presented headaches, beginning in the night at unspecified times, but always present at wakening, and always stopping at 10.30 h, despite therapy or different wakening times. The exact time of onset was not clearly specified, since the pain inconstantly awaked the patient from sleep, and sometimes he could fall, but the pain was always described as present at awakening.

The pain had the same characteristics as in the first bout. Associated symptoms/signs included photophobia, phonophobia and restless behaviour. No evidence of lacrimation, nasal congestion or rhinorrhoea was reported during the attacks in the second bout.

Each attack was followed by the onset of dizziness, lasting about 3 h.

At this stage the patient fulfilled the diagnostic criteria for episodic CH, having completed two bouts (8 and 2 months, respectively) with a 4-month remission in between (1).

The symptomatic treatments he was given [ketoprofen, paracetamol with codeine, metamizole, ketorolac, ibuprofen, oxygen (7–8 l/min, 10–15 min duration, administered through a non-rebreathing mask while sitting on bed), sumatriptan (6 mg subcutaneously) and octreotide (0.1 mg/ml subcutaneously] had no clear-cut effect, with the exception of oxygen, which showed partial efficacy on pain duration.

The patient underwent also consecutive trials of citalopram (4 mg/day), amitriptyline (6 mg/day, induction of aggressive behaviour), dexamethasone in association with cyproheptadine (4 mg + 4 mg/day, adverse events), verapamil (240 mg/day), topiramate (75 mg/day) without efficacy (Table 1). Therapy with lithium was proposed but the parents refused to give informed consent.

During the observation time, the patient continued to present two headache attacks per day, lasting from 50 to 60 min.

During the period March–May 2007 the patient was seen and followed up in another headache centre, where he was put on combination therapy with rivastigmine, methysergide, olanzapine, Al-Mg hydroxide and L-acetylcarnitine. This treatment continued for almost 2 months, with the exception of olanzapine (suspended after 1 week, for psychomotor agitation) and methysergide (suspended after 1 month, for psychomotor agitation). In April, the frequency was one attack/day and in May the period was over, with progressively decreasing attack duration (Fig. 2). Despite this temporal pattern, the patient was seen in the same headache centre and was again given rivastigmine, parenteral methylprednisolone (4 mg/day), chlorpromazine (6 mg/day) and

Table 1. Summary of prophylactic treatment used in our patient

Medication	Dose /day	Time	Efficacy	Reason of interruption
Citalopram	4 mg	~15 days	None	Inefficacy
Amitriptyline	6 mg	~20 days	None	AE: aggressiveness
Dexamethasone + cyproheptadine	4 mg + 4 mg	~1.5 months	Initial partial efficacy on intensity and attack duration	Relapse of episodes + AE (hyperphagia + gain of weight)
Verapamil	240 mg	~2 months	Partial–transient efficacy on attack duration	Inefficacy
Topiramate	Up to 75 mg	~1 month	None	AE: psychomotor agitation

AE, adverse events.

Table 2. Demographic data of published reports

Literature	(5 population studies) (12 case report – 18 patients) Two studies are both population + case reports
No. of patients	128 (110 + 18)
Age of onset (years)	11–14 (range: 3–18)
Pedigree	Positive for CH: ~10% Positive for migraine: ~25%
M : F ratio	M : F ~3.2:1 Range: 1:1–6:1
Episodic cluster/chronic cluster	Episodic (107/128)/chronic (21/128) Primary chronic in 6 patients
Duration of cluster headache bouts	From 1 week to 5 years
Frequency of cluster headache bouts	From 1/5–7 weeks to 1/6 months or unique
Frequency of headache attacks/cluster period	From 3/week to 10/day
Symptomatic treatment (no. effective/no. tried)	Oxygen (5/5) Sumatriptan (3/3) Ergotamine (2/2) Acetylsalicylic acid (1/3) Paracetamol (1/2) Ibuprofen (1/1) Indomethacin (0/1) Codeine (0/1)
Prophylactic treatment (no. effective/no. tried)	Pizotifen (3/3) Verapamil (3/3) Prednisone/prednisolone (2/2) Indomethacin (2/2) Methysergide (2/3) Flunarizine (1/1) Astemizole (1/1) Loratadine (1/1) Acetylsalicylic acid (0/1) Cyproheptadine (0/1) Propranolol (0/2) Amitriptyline (0/2) Biofeedback (0/1) Sinus surgery (0/1)

ranitidine (150 mg/day). On discharge, a therapy with rivastigmine, trimipramine, clonazepam and L-acetylcarnitine was tried for a period.

During all this period the patient has been followed in another headache centre. The therapies administered were all decided there, in agreement with parents.

When seen during the second bout, he was again started on a daily course with rivastigmine (0.75 mg/day), trimipramine (6 mg/day), verapamil (60 mg/day) and L-acetylcarnitine (1000 mg/day, oral), without efficacy as was in the first course. Parents had again refused therapy with lithium salts. The treatments administered in previous reports are shown in Table 2.

Since elements of psychiatric comorbidity were found in the medical history, a psychodiagnostic evaluation was performed. Psychological data were obtained from individual interviews, drawings, semi-structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version) and administration of projective tests (Rorschach, Blacky Picture Test). From both the interviews and the tests clear

components of anxiety appeared, especially regarding the separation from the parental figures, traits of obsessive-compulsive behaviour and an evident inhibition of phantasmatic activity, with a marked recourse to concreteness.

Moreover, during the second cluster period, there was more evidence of a secondary gain from the symptoms, such as a greater care from parents and other family members and a reduction in school activities.

In our opinion, the psychological picture does not affect the clinical pattern of our patient.

Discussion

To the best of our knowledge, there are 15 studies ($n = 128$), dealing with patients under 18 years [i.e. five population studies (110 patients) and 12 case reports (18 patients), considering that two studies are both population studies and case reports]. According to these studies, the prevalence of CH at paediatric age is estimated to be 0.09–0.1%.

The mean age of onset in paediatric age studies is 11–14 years, but the range could differ (i.e. 3–18 years), since several cases with onset under 10 years have been reported (5,6,8,10–20).

Genetic factors appear to be involved in the same proportion as in the adult population, as a pedigree positive for CH has been found in approximately 10% of cases, whereas a pedigree positive for migraine-type headache was found in 25% of cases. Male : female ratio seems to show almost the same proportion (M : F ~3.2:1) as in adulthood.

Prevalence of episodic and chronic forms shows the same values as at adult age (80–90% vs. 10–20%). No data have been reported about the incidence of primary chronic forms, although six probable cases have been described (8,11,13,17).

These patients could present a single cluster period, or recurrence of clusters, separated by periods from 5–7 weeks to 6 months. The frequency of headaches attacks could vary from 3/week to 10/day. In this perspective it has been noted that the frequency of headaches/cluster periods is smaller in childhood. Similarly, the duration of the single cluster period is shorter (3,5,8,11).

It has also been observed that the temporal pattern shows a trend towards a gradual increase of frequency and duration of symptoms in adult life; however, the number of patients reported is too limited to draw conclusions.

It has also been reported that autonomic symptoms and signs seem to be less evident in children than in adults, although these data need to be confirmed (11).

Several treatment alternatives have been tried in the different case reports. In all of them the first- or second-line medication always turn out to be effective. To the best of our knowledge, no case of pharmacoresistance has been reported. According to these data, the most effective symptomatic treatments are oxygen (11,13,15,17), sumatriptan (15,20) and acetylsalicylic acid (16,21). Prophylactic treatments tried in literature are prednisone/prednisolone (12,21), indomethacin (16), pizotifen (15), verapamil (15,17,20), methysergide (11,21,22), loratadine (23), astemizole (23) and flunarizine (14). No controlled study has been reported.

In comparison with the reported cases, our patient appeared to be resistant to the majority of the most effective symptomatic and prophylactic medications.

According to the criteria of the International Classification of Headache Disorders, 2nd edn (1), our patient should be considered as having episodic CH, but presents peculiar features different from other cases of CH in childhood reported in the literature. This patient could represent a 'variant' clinical picture.

First, a prolonged first cluster period (8 months) seems unusual; at the beginning of the disease, short cluster periods are more frequently described, with the exception of the primary chronic forms. In addition, the remission was rather short (4.5 months). This temporal pattern may suggest a trend to chronic form for our patient, but needs to be confirmed at forthcoming follow-up.

Second, our patient represents the first case of CH in childhood resistant to symptomatic treatment, even with adult doses. Besides, the efficacy of the therapy with rivastigmine, methysergide, olanzapine and L-acetylcarnitine in aborting the bout is questionable. The progressive reduction in duration of episodes resembles more a spontaneousremission of a cluster period than a therapy effect (Fig. 2).

Third, the young age of onset and the severity of pain (no different from adults) already at this stage is another aspect not reported in previous case reports.

The last atypical pattern of our patient is the autonomic involvement. The sense of heat in the area of pain without pain and inconstant autonomic signs represent a pattern in concordance with what is seen in adult dissociation between pain and autonomic symptoms and signs.

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Proposals for the organisation of headache services in Europe

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Abstract The mission of the European Headache Federation (EHF) is to improve life for those affected by headache disorders in Europe. Progress depends upon improving access to good headache-related health care for people affected by these disorders. Education about headache—its nature, causes, consequences and management—is a key activity of EHF that supports this aim. It is also important to achieve an organisation of headache-related services within the health systems of Europe in order that they can best deliver care in response to what are very high levels of need. This publication assesses this need, and sets out proposals for service organisation, on three levels, to meet the resultant demand.

Keywords Headache · Migraine · Headache centre · European Headache Federation

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Introduction

The mission statement of the European Headache Federation (EHF) sets out its primary purpose: to improve life for those affected by headache disorders in Europe [1]. EHF undertakes a range of activities in pursuit of this aim. "Educating Europe" about headache—its nature, prevalence, causes, consequences and management—is of highest importance. With knowledge of headache, and especially these aspects of it, comes recognition of headache disorders as a major public-health priority, and awareness of the need for effective solutions to them.

While EHF therefore puts much of its efforts into education [2], it does not neglect careful consideration of what these solutions should be, and how they might be implemented. Since better health care for headache and ready access to it are their essence, the organisation of headache-related services within the health systems of Europe becomes an important focus also, in order to maximise both effectiveness and cost-effectiveness. The reality is that levels of need for headache-related health care are very high.

This paper first assesses this need in Europe, and the demand likely to result from it. Then it sets out proposals for service organisation, on three levels, to meet this demand. It is the result of a collaboration between EHF and Lifting The Burden, the World Health Organization's

Global Campaign to Reduce the Burden of Headache Worldwide [3, 4], and of consensus meetings of experts in headache disorders who have particular interest in their public-health implications. In due course, these proposals will be formulated into recommendations to sit alongside other guidance produced by EHF [2, 5].

Headache-related health care needs assessment

According to epidemiological data, among every 1,000,000 people living in Europe there are 110,000 adults with migraine [6, 7], 90,000 of whom are significantly disabled [8]. There are 600,000 people who have occasional other headaches, the majority being episodic tension-type headache and not significantly disabling. And there are 30,000 with chronic daily headache [7], of whom most are disabled and many have medication-overuse headache.

It is reasonable to expect that at least everyone with disabling migraine or chronic daily headache is in need of (that is, likely to benefit from) good headache care. This means 120,000 adults, or 15% of the adult population. Empirical data from a large UK general practice support this: 17% of registered patients aged 16–65 years consulted for headache at least once in 5 years [9]. In addition, needs arise in the child population. There are few data on which to quantify these needs, but they are likely to arise at something like half the rate per head of adults (i.e., 15,000 children per 1,000,000 of the general population). Upon these statistics, with some assumptions, it is possible to make calculations of service requirements.

The numbers that these calculations generate show beyond argument that most headache services must be provided in primary care. This is not a bad thing: most headache diagnosis and management requires no more than a basic knowledge of a relatively few very common disorders, which ought to be wholly familiar to primary-care physicians. Only standard clinical skills, which every physician should have, need to be applied. No special investigations or equipment are usually necessary. Perhaps 10% of presenting patients might appropriately be treated in a specialist headache clinic. The empirical data from the UK general practice again support this: of the adult patients consulting for headache, 9% were referred to secondary care [9].

The first assumption is that "demand" for headache-related health care is expressed by only 50% of those in need (i.e., 50% who might benefit from medical care do not seek it). Further assumptions are that: (1) the minimum consultation need per adult patient in primary care is 1 h in every 2 years, 30 min for the first visit and 30 min in total for 1–3 follow-up appointments; (2) the minimum need per child patient in primary care is double the adult requirement (i.e., 1 h/year); (3) no wastage occurs in primary care through failures by patients to attend appointments; (4) at a specialist level, the minimum consultation need per adult patient in a year is 45 min for the first visit and 15 min in total for follow-up; (5) for children it is higher: say 1.25 h in total; (6) the need for inpatient management is very low (<1% overall of presenting patients) and can be ignored in these calculations; (7) no wastage occurs in specialist care through failures by patients to attend appointments, or it is discounted by overbooking; (8) 1 day per week of each medical full-time equivalent is the minimum requirement for administration, audit and continuing professional development; (9) each week therefore allows 4 days, each of 7 h, of patient-contact time, and 48 weeks are worked per year.

These assumptions are conservative. Despite that, the estimated service requirements expressed in medical full-time equivalents (Table 1) are very challenging. Headache services must be organised, or they cannot possibly be delivered efficiently or equitably.

Organisation of headache services

We suggest the following basis for organisation (Table 2), suitable for most European countries. It sets what are intended as minimum standards to be adapted in accordance with the national health service structure, organisation and delivery.

Table 1 Estimated service requirements to meet headache-related health-care demand in a population

Estimated number of adults/children with headache-care needs per 1,000,000 population (*n*)	Hours of medical consultation per week	
	Expected demand in primary care	Expected demand in specialist care
120,000/15,000	780 h 28 full-time equivalents	140 h 5 full-time equivalents

Table 2 Headache services organised on three levels

Level 1: Headache primary care	Accessible first contact for most people with headache Primary-care physicians[a] providing front-line headache services and acting as gatekeeper to
Level 2: Headache clinics	Run by trained physicians in primary or secondary care, referring when necessary to
Level 3: Academic headache centres	Specialist secondary-care, hospital-based

[a] And/or nurses plus pharmacists in some countries

Level 1: Headache primary care should meet the needs of 90% of people consulting for headache, and have referral channels to levels 2 and 3 as needed. Physicians at this level should competently diagnose and manage most migraine and tension-type headache, and recognise other common primary and secondary headache disorders listed as core diagnoses (Table 3). On the assumptions above, one full-time equivalent physician can provide headache care at level 1 for a population no larger than 35,000.

Level 2: Headache clinics should provide care to 10% of patients seen at level 1 who are referred to level 2. They should have a referral channel to level 3 as needed, and access to other services such as neurology, psychology and physiotherapy. Physicians at this level need to offer "special interest" services, in primary care or in secondary care outpatients, and competently diagnose and manage more difficult cases of primary headache and some secondary headache disorders (Table 3). One full-time equivalent physician can provide headache care at level 2 for a population no larger than 200,000.

Level 3: Specialist headache centres should provide advanced care to 10% of patients seen at level 2 who are referred to level 3, and support emergency or acute treatment services for patients presenting with headache. Physicians at this level need to offer specialist headache services in secondary care, with full-time inpatient facilities (minimum 2 beds/million population), and work in a multidisciplinary teams with access to equipment and specialists in other disciplines for diagnosis and management of the underlying causes of all secondary headache disorders. One full-time equivalent physician can provide headache care at level 3 for a population no larger than 2,000,000.

Table 3 ICDH-II core diagnoses to be recognised at level 1 [10]

Primary headache disorders
1.1 Migraine without aura
1.2 Migraine with aura
1.2.3 Typical aura without headache
2.1 Infrequent episodic tension-type headache
2.2 Frequent episodic tension-type headache
2.3 Chronic tension-type headache
3.1.1 Episodic cluster headache
3.1.2 Chronic cluster headache
Secondary headache disorders
5.2.1 Chronic post-traumatic headache attributed to moderate or severe head injury
6.2.2 Headache attributed to subarachnoid haemorrhage
6.4.1 Headache attributed to giant cell arteritis
7.2 Headache attributed to low cerebrospinal fluid pressure
7.4.1 Headache attributed to increased intracranial pressure or hydrocephalus caused by neoplasm
8.2 Medication-overuse headache (and sub-types)
13.1.1 Classical trigeminal neuralgia
13.18.4 Persistent idiopathic facial pain

Discussion

The organisation of headache services in Europe has been the subject of few publications [11, 12]. In the UK, the pattern of referrals has been described in detail by Dowson [13, 14]. Most patients who cannot be treated effectively in primary care are referred by their primary-care physicians to neurologists, but some may go to general practitioners with special interest (GPwSIs) in headache [15]. A few end up in specialised secondary-care or academic headache centres. While these options appear to reflect our three proposed levels, there is no formal organisation of services in this way. Much is ad hoc, and many patients do not progress from level 1 who would benefit from doing so. On the other hand, some patients are referred upwards who could, and should, be perfectly well managed by a primary-care physician. A similar approach is not used in other countries such Italy, Spain and France.

It is unfortunately true that the presence of a better, 3-level system in a health-care structure is likely to stimulate demand. But it should be recognised that this is simply unmasking need that is there already. It is crucial, within these proposals, that better knowledge of headache and the use of evidence-based guidelines [5] in primary care keep the great majority of patients at levels 1 and 2, reducing unnecessary demand upon more costly specialist care. This more rational use of health-care resources is the means by which effective care can reach more who need it.

There are, however, major implications for training. These need careful consideration. The start, though it is not easily achieved, is to give more emphasis to headache diagnosis and management in the medical schools undergraduate curriculum. This will ensure at least that newly-qualified doctors will have some understanding of a set of burdensome and very common disorders—which is often not the case now. But there will be much more to do beyond that if headache care, when delivered, is to be optimally effective at all levels. Within the 3-level care system proposed, a training role for each higher level to the level below can be envisaged. It is likely that the entire structure will depend upon these roles being developed.

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

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REVIEW

Meeting patient expectations in migraine treatment: what are the key endpoints?

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Abstract Clinical outcomes of migraine treatment are generally based on two major endpoints: acute pain resolution and effects on quality of life (QOL). Resolution of acute pain can be evaluated in a number of ways, each increasingly challenging to achieve; pain relief, pain freedom at 2 h, sustained pain-freedom, and SPF plus no adverse events (SNAE, the most challenging). QOL questionnaires help assess the burden of migraine and identify optimal treatments. Pain resolution and improved QOL form the basis of the ultimate target—meeting patient expectations, to achieve patient satisfaction. To achieve this, it is crucial to choose appropriate endpoints that re ect realistic treatment goals for individual patients. Moreover, SNAE can help discriminate between triptans, with almotriptan having the highest SNAE score. Kaplan–Meier plots are also relevant when evaluating migraine treatments. The use of symptomatic medication may lead to the paradoxical development of medication-overuse headache. In general practice, patients should use simple tools for pain measurement (e.g. headache diary) and a QOL questionnaire. A composite endpoint of pain resolution and QOL restoration would constitute a step forward in migraine management.

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Introduction

Migraine, other primary headaches, and chronic headache from overuse of medication have a major impact on sufferers and on society because of their high prevalence in both young people and adults and their negative consequences in terms of quality of life and work performance.

Migraine, as defined by the International Headache Society [1], affects about 18% of women and 6% of men in the United States [2, 3]. The intensity and duration of symptoms render many migraine sufferers unable to function or to perform work and leisure activities [3, 4]. Migraine has long been recognised as a major cause of work absenteeism and impaired productivity [5, 6] and productivity losses for migraine patients have been well documented [7].

No large studies have directly assessed patient satisfaction related to the treatment of migraine in primary care, partly because there are no objective endpoints for pain which is, by its nature, subjective. The classical approaches are based on two major endpoints: resolution of acute pain and effects on quality of life.

Traditionally the effects of symptomatic treatments are assessed by rating pain intensity, attack duration, and the presence/absence of accompanying symptoms. This information is obtained only retrospectively by interviewing the patient or using a headache diary.

Patient satisfaction with migraine treatment requires the rapid onset of pain relief, early complete relief, sustained pain freedom, relief of associated symptoms, consistent pain relief across attacks, the absence of side effects, a fast return to normal functioning and reduced disruption of daily activities [8].

Acute endpoints in migraine treatment

The advent of triptans, which are highly effective drugs for migraine treatment, stimulated the introduction of new endpoints for assessing migraine treatments. These include: (1) degree of pain relief (PR), (2) pain freedom at 2 h (PF), (3) sustained pain freedom (SPF = pain free at 2 h plus no use of rescue medication and no recurrence within 24 h) and (4) sustained pain freedom associated with no adverse events (SNAE) [9]. These endpoints allow us to measure treatment effects at different levels that are increasingly challenging to achieve. However, the choice of endpoint needs to re ect outcomes that are realistically achievable in individual patients, according to their illness profile. Each of these endpoints will be considered in turn, to examine their relative strengths and limitations as tools to assist in the measurement of outcomes relevant to patient expectations, and ultimately patient satisfaction.

Pain relief at 2 h measures the percentage of patients whose migraine pain intensity changes from moderate or severe prior to the start of treatment to mild or no pain after 2 h. However, even though pain relief is a desirable outcome, PR is an imprecise measurement because it combines patients who are pain free with those who have residual mild pain at 2 h.

Pain freedom at 2 h (2-h PF), on the other hand, requires all patients to be pain free at 2 h after dosing, regardless of baseline pain, and as such is a more robust outcome measure. Nevertheless, 2-h PF takes no account of what happens after 2 h. This is an important issue when comparing two treatments because, while both may have a high 2-h PF rate, one may be associated with a greater recurrence between 2 and 24 h after dosing. Thus, this outcome measure is unable to distinguish between treatments for an attribute which is sought by patients, namely sustained pain relief.

Sustained pain freedom (SPF) addresses the limitations of the 2-h PF endpoint, and is now widely regarded as an outcome that more closely represents patient expectations. This is because it encompasses 2-h PF, but extends the requirements such that no rescue medication and no headache recurrence between 2 and 24 h after dosing are allowed.

SPF with no adverse events (SNAE) goes a step further, taking into account tolerability in addition to the efficacy of treatments.

Pain severity and timing of treatment intake

This issue of pain severity raises another important consideration; timing of treatment intake in relation to the time of onset of the migraine attack.

Traditionally, patients are instructed to take medication when their baseline pain has reached moderate-severe intensity. This is particularly the case in classical clinical trials because it allows measurement of changes from a high baseline, which increases the likelihood of distinguishing between treatments, notably between active and placebo interventions. This is relevant because the placebo-response in migraine patients is usually high [9, 10].

Moreover, outside the clinical trial setting patients often wait until their headache has reached moderate-severe intensity before starting treatment. They do this for a variety of reasons. One study found that most commonly it was because patients wanted to wait and see if it was really a migraine attack, or only wanted to take medication if it was a severe attack [11]. Other reasons patients gave included concerns about side effects, concerns about drug effectiveness if it was taken too frequently, and worries about the risk of becoming dependent on the drug [11].

In contrast, the 'Act when Mild' paradigm advocates the intake of migraine medication before acute pain has reached moderate-severe intensity and/or as soon as possible after the onset of symptoms [12]. This paradigm is supported by a growing body of evidence [12]. In particular, the Act when Mild (AwM) study with almotriptan 12.5 mg provides the most recent and most robust evidence that the early intake of medication (i.e. while migraine pain is still mild, and within 1 h of onset of the migraine attack) is associated with important benefits compared with delaying intake until pain has reached moderate-severe intensity [12]. Table 1 summarises how the AwM study outcomes address patient expectations of treatment. Compared with delaying intake of medication, taking almotriptan 12.5 mg early—before the acute attack has peaked—is more likely to provide outcomes that meet most of patient expectations.

How do the AwM study endpoints meet patient expectations?

The limited ability of different endpoints to distinguish between treatments is illustrated in a recent paper by Ferrari and colleagues about a meta-analysis of 53 triptan studies involving over 24,000 migraine patients (Table 2) [13]. The endpoints used in this meta-analysis were pain relief at 2 h, SPF, consistency of effect over more than one migraine attack, and tolerability. Several features of this meta-analysis are notable. First, comparisons were made between sumatriptan 100 mg as the point of reference and 5 other triptans—almotriptan, eletriptan, naratriptan, rizatriptan, and zolmitriptan. Secondly, a tendency to a dose–response pattern was apparent for sumatriptan, eletriptan, and rizatriptan across the different endpoints. The

Table 1 How the AwM study results meet patient expectations. Adapted from [12]

Patients-sought attribute of treatment	AwM study outcome variables (still mild vs. moderate-severe)[a]
1. Complete relief	1. Increased 2 h pain-free status
2. Fast onset of pain relief	2. Shorter duration of migraine attack
3. Rapid restoration of normal functioning	3. Faster achievement of pain-free status
4. Relief of associated symptoms	4. Early pain relief within 0–2 h[b]
5. No recurrence	5. Reduced duration of migraine pain
6. Absence of side effects	6. Less time lost in daily activities
	7. Reduced nausea, vomiting, phono-photo- and osmophobia
	8. Higher sustained pain-free state
	9. Less use of rescue medication
	10. Placebo-like safety and tolerability

[a] Points 1 and 3 column on the right show only a trend to significance, points 4, 7, 9 not covered in [12] but could be evidence

[b] Measured in mild-moderate pain for almotriptan versus placebo

Table 2 Comparison of triptan outcomes with sumatriptan 100 mg

	Pain relief at 2 h	Sustained pain free	Consistency	Tolerability
Sumatriptan 25 mg	−	−/=	−	+
Sumatriptan 50 mg	=	=	−/=	=
Almatriptan 12.5 mg	=	+	+	++
Eletriptan 20 mg	−	−	−	=
Eletriptan 40 mg	=/+	=/+	=	=
Eletriptan 80 mg	+	+	=	−
Naratriptan 2.5 mg	−	−	−	++
Rizatriptan 5 mg	=	=	=	=
Rizatriptan 10 mg	+	+	++	=
Zolmitriptan 2.5 mg	=	=	=	=
Zolmitriptan 5 mg	=	=	=	=

Derived from a meta-analysis of 53 trials involving 24,089 patients [12]. Data for frovatriptan unavailable. Reprinted from Ferrari et al. (2001) *Lancet* 358:1668–1675. With permission

− Inferior to Sumatriptan 100 mg, = equivalent to Sumatriptan 100 mg, + superior to Sumatriptan 100 mg

outcomes for pain relief and SPF were generally similar for each individual triptan, suggesting either that there was consistency across treatments for these endpoints, or that neither of these endpoints was sensitive enough to distinguish differences between the drugs. There were greater differences between triptans for tolerability, assessed as adverse events, than for measures of efficacy [13]. This is an important observation, because 'absence of side effects' is a key treatment attribute sought by migraine patients. Therefore, the composite endpoint of SPF plus no adverse events (SNAE) has been proposed as a relevant outcome measure [9]. This is the most challenging endpoint to achieve because it combines multiple outcome criteria, namely 2-h PF, plus no use of rescue medication, plus no recurrence within 24 h of dosing, plus the absence of side effects.

The SNAE is the most challenging endpoint to achieve can be seen from a recent analysis of comparative outcomes of treatment with almotriptan 12.5 mg in triptan-naive (TrN) versus triptan-experienced (TrE) migraine patients (Fig. 1) [14]. This was a post hoc analysis in migraine patients with moderate-severe pain intensity at the time of treatment, in which the endpoints of 2-h pain relief, 2-h PF, SFP and SNAE were analysed. The results indicated that although SNAE is the most challenging outcome, approximately one-third of patients treated with almotriptan 12.5 mg achieved it. Moreover, this was the case whether patients were TrN or TrE, indicating a high level of benefit from almotriptan regardless of triptan history. However, this analysis has a limited value due to the absence of a comparator group.

In order to address this point, we can consider the in uence of SNAE on the outcomes reported in the meta-analysis of Ferrari and colleagues [13]. Based on SPF and AE rates calculated for different triptans, eletriptan 20 mg was associated with the lowest SPF rate (although this is attributable to the fact that this is now recognised as a sub-therapeutic dose), and almotriptan 12.5 mg had the highest SPF rate [9]. Eletriptan 80 mg, a higher-end dose of this triptan, was associated with the highest incidence of AEs, and almotriptan 12.5 mg the lowest incidence (Fig. 2).

Expressing these data graphically shows a clear pattern of a dose–response effect for sumatriptan, eletriptan, rizatriptan, and zolmitriptan for both SPF and AE (Fig. 2). It is

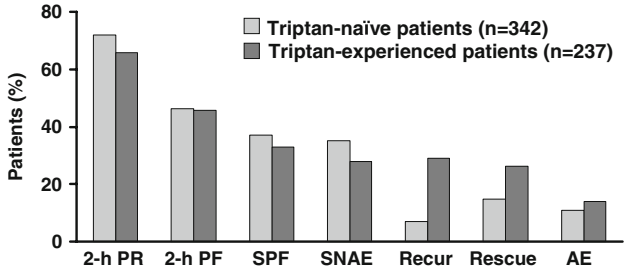

Fig. 1 Almotriptan in triptan-naive versus experienced patients (treated with almotriptan 12.5 mg) after Pascual et al. [14] with permission. *2-h PR* pain relief at 2 h, *2-h PF* pain-free at 2 h, *2-h SPF* sustained pain-freeat 2–24 h without rescue medication, *SNAE* sustained pain-free and no AEs, *Recur* headache recurrence at 24 h, *Rescue* rescue medication 2–24 h,*AE* adverse event

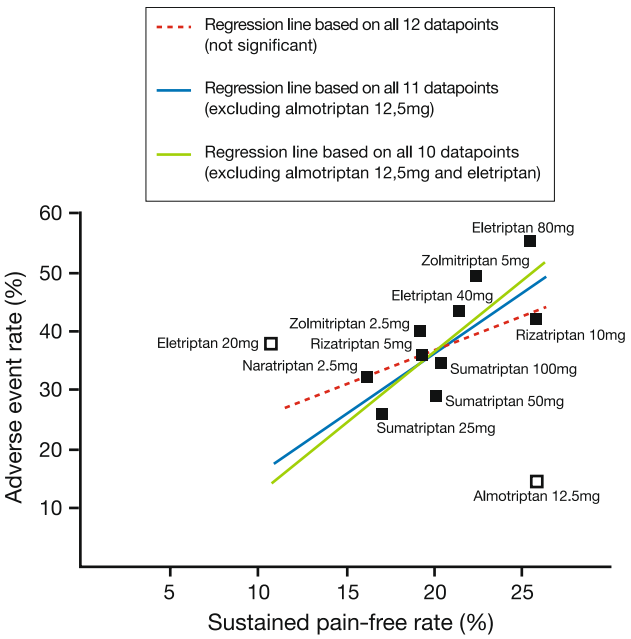

Fig. 2 SPF versus adverse event rates for different triptans. Derived from a meta-analysis of 53 trials involving 24,089 patients [9]. Data for frovatriptan unavailable. After Dodick et al. (2007) *CNS Drugs* 21 (1):73–82 with permission. *A* Almotriptan, *E* eletriptan, *N* naratriptan, *R* rizatriptan, *Z* zolmitriptan

also clear from this graph that almotriptan 12.5 mg is an outlier because of its high efficacy combined with its good tolerability. Statistical analysis and logistic regression confirmed that higher SPFs were strongly associated with higher AE rates, with the notable exception of almotriptan 12.5 mg [9]. Using these data, SNAE was calculated for each triptan dose under the base-case assumption of independence between efficacy and tolerability. The highest SNAE rate was for almotriptan 12.5 mg (22.2%). The analysis also showed that almotriptan had an 88% probability of being superior to sumatriptan 100 mg in terms of SNAE across all values for the efficacy–tolerability relationship for these triptans. The SNAE therefore not only incorporates treatment attributes that are relevant to patient satisfaction, but is also a useful measure for discriminating between migraine therapies.

Other endpoint measures and migraine assessments

As well as the use of 'traditional' endpoints to assess outcomes of migraine treatment, a number of other issues need to be considered in order to provide a broader picture of patient progress.

Headache-related disability associated with migraine is poorly recognised in clinical practice, often leading to the use of ineffective care strategies, and an apparently poor outcome. Evaluation of the level of migraine-related disability is crucial to enable effective treatment decisions to be made; for example, between stepped care versus stratified care, as described by Diener et al. [15].

As migraine is a chronic illness, recurrent attacks can have a negative impact on health-related QOL (HRQOL) because each attack, as well as the anticipation of an attack, can interfere with a migraineur's ability to work, enjoy daily activities and interact socially. Therefore, measurement of HRQOL in migraine patients is needed to provide a more complete picture of the progress of the patient beyond the clinical symptoms associated with migraine.

Medication-overuse headache (MOH) can develop from frequent, and sometimes excessive, use of pain medications. It is important, then, that with the availability of a variety of migraine medications, both over-the-counter and on prescription, a record of medication use is kept. This can help identify or discount MOH as a contributory factor to headache recurrence in migraineurs, which is important as otherwise MOH may limit optimal outcomes.

Lastly, Kaplan–Meier plots, sometimes called survival curves, can be used as a graphically visual display of pain outcomes in migraineurs that can be relevant when evaluating different interventions.

These measures will be considered in more detail.

Disability

The *Migraine Disability Assessment* (*MIDAS*) *Questionnaire* was developed to assist rational treatment decisions and evaluate progress [16]. Migraine sufferers answer five questions that assess time lost in days due to headaches in three domains covering the previous 3-month period. The three domains include employment (paid work or school), household work, and family/social/leisure activities. The MIDAS score is the sum of the answers to the five questions. Another two questions (A & B) are not scored but

provide the physician with clinically relevant information on attack frequency and pain severity.

Its ease, simplicity, high consistency and reliability support the use of the MIDAS Questionnaire in everyday clinical practice. The MIDAS grades provide an intuitive means of representing headache-related disability. MIDAS is an effective tool to improve communication between patients and healthcare professionals. As it assesses headache-related disability and provides information on headache frequency and pain intensity, it can be used to increase awareness of, and highlight problems associated with, migraine. MIDAS can be used as a screening tool to help physicians provide appropriate treatment at the patient's initial consultation based on level of disability. Patients who present with a high MIDAS score may require referral to specialist physicians for a more detailed diagnosis.

The change in MIDAS score during treatment can also be used to monitor therapeutic response to treatment and patient progress over time. MIDAS can be used to support public health initiatives, such as evaluating the true extent and costs of migraine, which may be underestimated by healthcare professionals and payers.

HRQOL

The use of HRQOL as an endpoint measure of migraine treatment is based on the presence of a wealth of literature describing the effect of the chronic nature of migraine on HRQOL [17, 18]. Its high burden has been likened to that of osteoarthritis and diabetes mellitus, and the high prevalence of migraine adds to the socioeconomic burden [17, 18].

Two types of questionnaire have been used to measure HRQOL: general and disease-specific instruments. General QOL scales assess a number of activities within physical, social, psychological and behavioural life domains. Disease-specific instruments re ect particular limitations or restrictions associated with specific disease states [9] and can evaluate changes over time. There are three main instruments: migraine diaries, migraine-specific HRQOL instruments and the Short Form Health Survey (SF-36).

With the *migraine diary* one can rate headache severity (none, mild, moderate, severe) functional disability (none, mild, severe, bed rest) and associated symptoms (nausea, vomiting, photo/phonophobia). Paper and electronic diaries are available [19].

Migraine-specific HRQOL (*MS-HRQOL*) instruments are available to evaluate changes over time in work and social functioning, energy/vitality, symptoms and feelings/concerns. While these outcomes are not acute symptom-specific, they measure the effect on QOL of changes in symptoms across multiple attacks over time, and so enable a longer term perspective of the wider effects of a treatment paradigm to be assessed [20, 21].

The *Short-Form Health Survey* (*SF-36*) is a general health survey questionnaire (i.e. not migraine-specific) consisting of eight domains, each scored from 0 (worst possible outcome) to 100 best possible outcome [22]. Completion of the SF-36 at specified intervals throughout the course of the migraine illness can monitor changes in QOL over time and so identify areas that may require closer clinical attention that would not be identified using traditional acute symptomatic endpoints [10].

However, just how sensitive these QOL instruments are at detecting clinically significant changes over time is not entirely clear and, although these instruments are useful endpoints for migraine clinical trials, their role in clinical practice is yet to be established [12].

Medication-overuse headache

Another issue that can in uence endpoints in migraine treatment is MOH [1]. The 2004 International Headache Society criteria guidelines state that MOH can be associated with the use of simple analgesics (aspirin or paracetamol), combination analgesics (containing caffeine, codeine or barbiturates), opioids, ergotamine or triptans, if taken for more than 10 days (15 days for simple analgesics) in more than 3 months.

Medication-overuse headache is currently a 'hot topic' in migraine treatment, not least because several issues associated with MOH can have an impact on migraine treatment endpoints. There is current ongoing debate about whether medication overuse is a cause or a consequence of chronic daily headache. The incidence and prevalence of MOH is not clear, because the definitions of MOH have, until recently, been unclear. Moreover, physician–patient communication is not always at a level that identifies this issue, since a diagnosis of MOH can only be made after the patient has stopped taking the medication. Susceptible individuals have a pre-existing episodic headache condition (most frequently migraine or tension-type headache) and the frequent (maybe daily) use of the analgesics referred to earlier 'transforms' the headache into one that occurs daily.

The characteristics of MOH include an increased frequency of headaches over time (without the patient being aware), waking with a headache in the morning which was not a feature of the original headache type, headache lacking features specific to migraine or tension-type headache, and headache occurring more easily after stress or exertion so that greater doses of medication are required to alleviate the headache. In addition, headaches recur within a predictable period after the last dose of medication, usually with reduced efficacy.

The goals of management in MOH are to identify any comorbid conditions driving the MOH, educate the patient, withdraw daily treatment (to restore an episodic headache pattern), and (re)establish an effective treatment strategy with acute and preventative medications [23–25].

Displaying endpoints

Finally, differing methods of displaying study endpoints can provide different views of the results. The data on duration of migraine attack presented by de Klippel for the AwM study provide an example [11]. Using a traditional bar chart, the mean duration was significantly shorter if almotriptan was taken when pain was still mild and within 1 h of pain onset compared with delaying treatment until pain was moderate-severe (2 vs. 5 h, $P < 0.0005$) (Fig. 3a).

However, displaying the results in this way tells us nothing about the evolution of differences over time. In contrast, if the results are displayed as a Kaplan–Meier plot (Fig. 3b), this alternative visual display enables us to see the evolution of the differences over time, which emphasises the benefits of the early intervention in migraine.

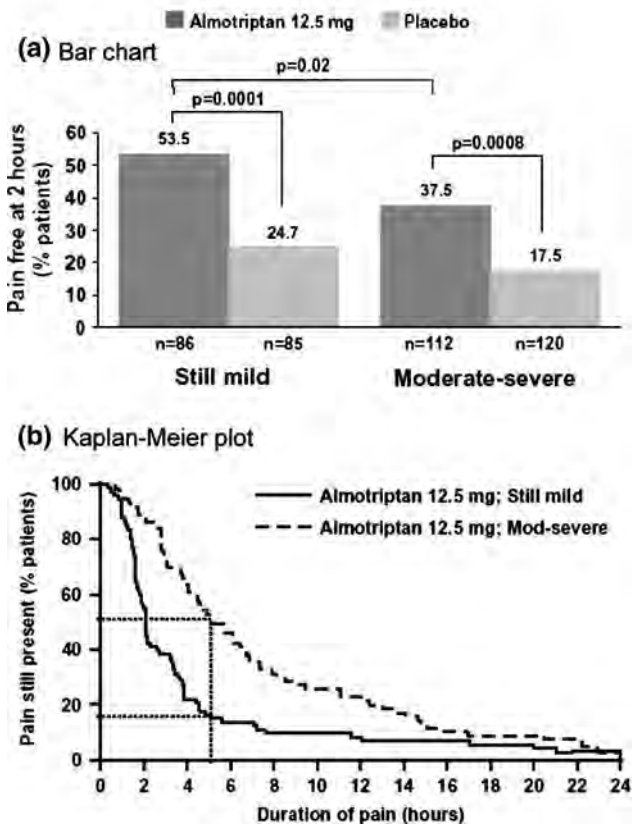

Fig. 3 Choice of method of endpoint display. Data from AwM study: duration of migraine attack for early treatment (still mild) versus delayed treatment (moderate-severe) [12]. After De Klippel. **a** Bar chart. **b** Kaplan–Meier plot

Conclusion

Traditional acute endpoints that evaluate migraine treatment need to be selected to best re ect individual patient expectations. Of these endpoints, SNAE appears to be the most challenging but also the most discriminating. To provide a complete picture, additional endpoints need to be taken into account. For example, the impact of migraine-related disability (e.g. MIDAS), the effect on HRQOL (e.g. MS-HRQOL, SF-36), and the risk and consequences of medication overuse should be considered. In addition, consideration should be given to the visual impact of endpoint displays; an appropriate figure can provide an intuitively simple overview of progress. For example, Kaplan–Meier plots can visually differentiate between interventions over time. In the future, a composite endpoint of pain resolution and QOL restoration would constitute a step forward in migraine management.

Conflict of interest None.

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INTRODUCTION

Physical therapy and exercise in headache

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Dealing with cervicogenic headache in a clinical setting requires, possibly one or more, therapeutic options for the patient. Cervicogenic headache is becoming an accepted clinical syndrome in which headache pain is thought to originate from the cervical spine. Unfortunately, there are no diagnostic imaging techniques of the cervical spine and associated structures that can determine the exact source of pain. Therefore, diagnosis and treatment are based on the major accepted criteria of clinical presentation and the use of diagnostic nerve blocks to identify the source of the pain generator before considering further interventional or neuroablative treatment. This suggests that consistent reproducible anatomic and neurophysiologic pathways exist for the reproduction of typical clinical pain patterns and the ability of neuroblockade to consistently interrupt these pain pathways.

However, a conservative therapeutic option should be attempted first. In this respect, physical therapy and exercise may provide a non-invasive approach to the 'neck factor' that may be involved in the pathogenesis of cervicogenic headache.

Neural blockade plays an essential role in the diagnosis and treatment of cervicogenic headache. A positive or negative response to a diagnostic nerve block must be considered in conjunction with the complexity of the patient with chronic headache, the placebo effect, and concurrent medical therapy, before proceeding with more invasive interventional or neuroablative treatment.

Clinical expertise, a high degree of technical skill, profound knowledge of the anatomy of the cervical spine, and an understanding of the pathophysiologic mechanisms of cervicogenic headache, are essential to have before performing these invasive procedures.

In addition to acknowledging the difficulty of performing randomized, double-blind, controlled surgical trials, we should be in agreement that further studies need to be done if interventional techniques are to become standard and accepted therapies.

In this section the conservative therapeutic approach and the major interventional, anaesthetic and ablative techniques for cervicogenic headache are reviewed.

Conflicts of interest

FA has served as a speaker for Almirall and is on the advisory board of Almirall.

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TUTORIAL

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Lessons from placebo effects in migraine treatment

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Abstract In medical research, the placebo effect is an important methodological tool. Placebo is given to participants in clinical trials, with the intention of mimicking an experimental intervention. The "nocebo" effect, on the other hand, is the phenomenon whereby a patient who believes that a treatment will cause harm actually does experience adverse effects. The placebo effect strongly influences the way the results of clinical trials are interpreted. Placebo responses vary with the choice of study design, the choice of primary outcome measure, the characteristics of the patients and the cultural setting in which the trial is conducted. In migraine trials, the placebo response is high, in terms of both efficacy and side effects. Although medical ethics committees are becoming increasingly resistant to the use of placebo in acute migraine trials, placebo nevertheless remains the pivotal comparator in trials of migraine medications.

Keywords Placebo • Migraine • Triptans • NSAIDs • Nocebo

Introduction

The word "placebo", which literally means "I shall please", derives from the Latin *Placebo domino in regione vivorum* ("I shall please the Lord in the land of the living"). It was first used in the 14th century in reference to hired professional mourners at funerals and thus had associations with the ideas of depreciation and substitution [1]. Around the same time, Chaucer in *The Canterbury Tales* (*The Merchant's Tale*) depicts a wicked, parasitic and sycophantic character, whom he calls Placebo [2]. Much later, placebo came to mean a substance that can be given to humour or gratify a patient rather than to exert a genuine pharmacological effect.

The first recorded medical dictionary definition of placebo refers to "a commonplace method or medicine", commonplace meaning common and pedestrian. Indeed, in Motherby's 1795 dictionary, placebo was defined as "a commonplace method or medicine calculated to amuse for a time, rather than for any other purpose" [3]. This definition was maintained until 1937, when Taber's Digest of Medical Terms [4] defined placebo as an "inactive substance" and a "substitute for medicine given to deceive the patient".

Although a placebo is still regarded as an "inactive" substance, its impact can be profound. In clinical trials, if its effects are not measured, the placebo response may obscure a true pharmacological effect of an active comparator.

Psychological mechanisms

There are at least four psychological mechanisms associated with the placebo response: (1) expectation, (2) conditioning, (3) therapeutic relationship and (4) empowerment [5]. Patients' expectations are based on their cultural background, on information given by the physician (dosage schedule, careful explanation of advantages and disadvantages) or written instructions, and on physical aspects of the placebo (colour, shape, taste, formulation). The old conditioning effect discovered by Pavlov is connected with displaying of the treatment: if symptom relief occurs following the administration of a particular tablet, the relief will, over time, become conditioned to occur following use of that particular tablet. There is also considerable evidence that a patient's interpersonal relationships play an important role. Social support influences a range of physiological parameters (heart, glands, immune system) and it provides a buffer against stress. Therefore, a patient-centred physician–patient relationship (e.g., proper interview conducted in a warm and friendly manner) is likely to produce a better outcome than a formal consultation. Last but not least, the placebo response is associated with empowerment, that is, the process of encouraging the patient to take an active part in the decision-making process regarding his treatment.

As all these factors can influence, to different extents in different patients, the size, variability and duration of a placebo response, this response becomes difficult to predict in advance.

Neurobiological mechanisms

Recently, there has been renewed scientific and public interest in the placebo effect following the publication of studies of its biological substrates. A placebo, through raised expectations and/or conditioning, can reduce pain by both opioid and non-opioid mechanisms. In the first case, placebo analgesia is typically blocked by the opioid antagonist naloxone, whereas in the second case it is not [6]. Central respiratory structures in the brainstem may also be inhibited by endogenous opioids as well as by placebo. The beta-adrenergic sympathetic system of the heart may also be inhibited during placebo analgesia, although the underlying mechanism is not known (reduction of the pain itself and/or direct action of endogenous opioids). Cholecystokinin [7] antagonises the effects of endogenous opioids, thereby reducing the placebo response. Placebo can also act on 5-HT-dependent hormone secretion, at both pituitary and adrenal gland level, thereby mimicking the effect of triptans.

There is evidence that the endogenous opioid system is implicated in the mediation of placebo effects under conditions of expectation of analgesia [8]. Using functional magnetic resonance imaging to measure, indirectly, neuronal activity during the administration of placebo with expectation of analgesia, Wager et al. [9] showed a significant effect on the activation of the μ-opioid system (dorsolateral prefrontal cortex, rostral anterior cingulate, left nucleus accumbens and right anterior insula). PET studies have shown that in painful conditions placebo will activate the same central structures of the pain matrix as opioids [10].

Placebo and headache

According to the International Headache Society (IHS) [11], controlled trials of acute migraine medication should be carried out "in accordance with the principle of the Declaration of Helsinki" [12]. Later on, however, the same IHS guidelines explicitly recommend the use of placebo in trials of abortive medications. Therefore, a contradiction arises, as the declaration of Helsinki states that when an effective treatment for a disease exists, it is unethical to assign patients in a research study to a treatment known to be less effective. But standards for the acceptable use of placebo in clinical trials are changing. It is now necessary to provide ethical and scientific justification for the use of placebo in some therapeutic areas. The use of placebo in trials of acute medication is generally regarded as justified in situations in which withholding the best current treatment will result in only temporary discomfort and no serious adverse effects. In addition, most protocols allow the use of rescue medication two hours after intake of study medication.

Placebo and migraine

It is well known that the placebo response in clinical trials of acute migraine treatments is widely variable, ranging from 6% to 47% of patients. It has thus been recommended that active drugs for migraine must be shown to be significantly superior to placebo [12].

Bendtsen et al. [13] evaluated the placebo response in placebo-controlled randomised clinical trials of analgesics in migraine attacks that fulfilled the IHS criteria. Eleven studies were included in their review. A "headache response" (i.e., defined as a proportion of attacks that decreased in pain severity from moderate–severe to mild or no headache within 2 h) was obtained after treatment

with placebo in 30% (mean) of migraineurs, although the range (variability) was large (7%–50%). Pain-free rates two hours after treatment with placebo were lower (mean 9%, variability 7%–17%), suggesting that that this is a more robust outcome measure.

Loder et al. [14] reviewed literature reports (1991–2002) of placebo-controlled trials with triptans in acute migraine, and found 31 trials that met their inclusion criteria. The mean proportion of patients with a headache response to placebo at 2 h was 28.5±8.7% (range 15%–50%), while the mean proportion of patients with a pain-free response to placebo at 2 h was 6.1±4.4% (range 5%–17%).

Placebo response in children and adolescents with migraine presents a particular challenge, not least because placebo rates are enhanced in this age group [14]. Lewis et al. [15] reviewed the limited available data on the use of analgesics and triptans in placebo-controlled trials of migraine in children and adolescents and found a large variability in the placebo response: present in 37%–53% of patients treated with placebo analgesics/non-steroidal anti-inflammatory drugs (NSAIDs), and in 28%–65% of those treated with placebo triptans. This explains why most trials investigating the efficacy of triptans in children and adolescents have failed to obtain conclusive findings [16]. As the response rates to triptans, however, were comparable with those found in adults, the variability of the placebo response must be taken into account, as must strategies to minimise it. One possibility could be to treat consecutive attacks with a placebo, which will likely show a decreasing response over time [17].

The "nocebo effect"

Although placebo response is used as an efficacy outcome, placebo is also associated with a spectrum of adverse events, reported across placebo-controlled clinical trials – the "nocebo" effect [18].

In a review of 109 double-blind, placebo-controlled drug trials involving a total of 1228 healthy volunteers, adverse effects were spontaneously reported by an average of 19% of those on placebo [19].

The following are examples of adverse effects that have been reported in patients receiving placebo, in placebo-controlled trials (any indication): drowsiness, fatigue, unsteady gait, mental confusion, motor retardation, insomnia, nervousness, motor agitation, headache, nausea, vomiting, constipation, diarrhoea, vertigo, dry mouth, leucopenia and death. In view of this, there is clearly a need to attempt to disentangle adverse effects associated with placebo from those associated with active medications, in order to arrive at a more accurate profile of the tolerability and safety of the active medication. In placebo-controlled trials of migraine, adverse effects may occur with placebo in >30% of patients [19], and in triptan trials the mean (±SD) proportion of patients reporting an AE on placebo was 23.4±14.1% (range 5%–74%) [20].

As placebo response rates in clinical trials in migraine may vary with different study designs, primary outcome measures and patient characteristics, and considering that the magnitude of the placebo effect can be influenced by a patient's expectations (conditioning), the severity of the pain at baseline and the rate of spontaneous resolution, placebo-subtracted outcome data may provide a more accurate profile of the active medication [13]. Adverse events with placebo triptans in migraine tend to be lower in European compared to North American studies [13], while within Europe, placebo response rates are higher in southern countries than in Scandinavia.

Even so, there are, inevitably, exceptional cases, as shown by the interesting report by Pascual-Lozano et al. [21], of a patient whose migraine, repeatedly refractory to analgesics, NSAIDs, ergotamine and opioids, responded well and consistently to placebo.

Potential lessons to be learned from placebo-controlled trials in migraine

Placebo response rates vary in studies presenting different designs, primary outcome measures and patient characteristics [12, 13]. However, the magnitude of these placebo effects in relation to active treatment does not justify the rate of spontaneous resolution, patient expectations (conditioning) and the severity of pain at baseline [12]. Furthermore, the lack of difference between a standard and a novel comparator does not prove the efficacy of the latter in the absence of a placebo group [10–12]. In addition, adverse events can only be appreciated when a placebo group is present. It has been shown that even though active drugs may be effective, a high placebo response rate may confound the evidence [18], and a high placebo response rate has been found to correlate with a high response on the corresponding active drug [12]. At the present time, comparison of results across trials is dangerous [12]. Placebo-subtracted data enable a more rigorous comparison across different trials.

In summary, although medical ethics committees are becoming increasingly resistant to the use of placebo in acute migraine trials, placebo remains the pivotal comparator in trials of migraine medications.

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The management of headaches in the emergency department: critical issues

Abstract Typical cases of the most common kinds of headache can be diagnosed and treated by general practitioners (GPs). Non-traumatic patients with *de novo* acute sudden-onset disabling headaches as well as significant worsening of pre-existing headaches seek care at emergency departments (EDs) and represent a diagnostic challenge for the consultant neurologist, who is the specialist of reference for the entire diagnostic process. Explicit diagnostic criteria for the classification of headache disorders (ICHD-II) are fundamental for verifying the final diagnosis, but in the emergency setting diagnostic and therapeutic guidelines and recommendations, coupled with lists of diagnostic alarms and warnings, may further contribute to the preliminary identification of secondary headaches.

Key words Secondary headaches • Emergency department • Diagnostic alarms • Guidelines and recommendations

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Introduction

The management of patients with severe/disabling headaches in the emergency department (ED) represents a diagnostic and therapeutic challenge for ED physicians and in particular for the consultant neurologist, who is the specialist of reference for almost all cases of *de novo* and non-traumatic headaches throughout the entire diagnostic process, from early observation following admission to the final discharge from hospital.

The significant amount of epidemiological data so far available on this topic has indeed contributed to a better definition of the many aspects which are relevant for clinical practice: prevalence of severe headache as a presenting symptom in EDs, relative frequency of primary *vs*. secondary forms and respective diagnoses, resources and costs involved in the diagnostic process, diagnostic accuracy and clinical outcome. However, due to the methodological problems arising from the epidemiological investigation in the emergency setting (namely the scarcity of controlled studies) only few effects have been produced by the results of the many studies available, on the everyday clinical practice, which remains heterogenous and lacking of structured references for a well-defined and validated approach.

The ICHD system [1] is indeed the most reliable and complete instrument for a correct diagnosis, but we do not yet know its effective contribution to the differential diagnosis of *de novo* headaches and the real perspectives of its applicability in the emergency setting.

The present contribution will, therefore, critically review the most recent data from descriptive epidemiology, in search of reliable methods for future observational prospective studies. Also, the available diagnostic and therapeutic guidelines and recommendations will be described briefly; thereby we will also take into consideration our data concerning the possible role of the so-called Diagnostic Alarms (DA) and "warning symptoms" in increasing the alertness of the physician and in reducing the risk of underestimating (and underinvestigating) "possible" symptomatic cases.

Headache prevalence in the ED

Headache as a symptom accounts for 1–3% of total admissions to EDs and the variability within this range is probably generated by external factors, namely the general efficiency of the health care system and, in general, the distribution in the territory of ED and specialist facilities.

Prevalence data, however, do not show significant differences among different sources with regard to the type of studies, i.e., retrospective *vs*. observational/prospective.

It has also been shown that the frequency of primary headache is lower in EDs than in the general population. But the most important differences emerge by the comparison between studies in the ICHD era and previous reports, in which migraine headaches were significantly underdiagnosed *vs*. tension-type headaches [2].

Regarding the Italian experience, data from retrospective studies [3] show a cumulative prevalence of 0.6% for primary headaches in EDs, while in observational and prospective studies the prevalence ranges from 1.2 to 2.35% of all ED attendances [4, 5]. Secondary headaches [4, 5] show a slight prevalence *vs*. primary forms or a balance, depending on the criteria adopted (exclusion of head traumas/paediatric cases, etc.). At discharge from ED the prevalence for migraine varies from 15 to over 30%; most primary headaches patients, however, are discharged with a diagnosis of headache "not otherwise specified" (NOS). A slight prevalence of secondary headache (56%) is reported by Luda et al. [6] with rough information about the diagnostic procedures performed in a small group of consecutive observations. A more recent original Italian study has investigated the degree of agreement between ED physicians and neurologists in evaluating a significant series of headache patients [7]. A lower agreement was found for cases presenting with a first attack (*de novo* headache); the Authors used a headache specialist as external standard of reference. From this perspective the experience from Cerbo et al. [4] is of particular interest because it confirms the low accuracy of ED physicians and the importance of providing a follow-up visit to a headache specialists for a final diagnostic definition according to ICHD-2004 criteria [1]. These studies also demonstrated that primary headaches in EDs are those with the most severe and frequent attacks (treatment refractory and disabling migraine, status migrainosus, cluster headache and TACs). Many authors have also discussed the problems related to the therapeutic approach, stressing the need for guidelines for the symptomatic relief of headache in the ED.

Critical issues in the evaluation of acute headache

Secondary headaches due to life-threatening intracranial disorders (SAH and other potentially fatal conditions) account for about 5% of the cases. The crucial elements for a differential diagnosis are found by examining the clinical characteristics of the headache picture and by looking for the eventual association of neurological and somatic signs/symptoms, as well investigating the personal and family history (main comorbidities and RFs). Typical cases of the most common kinds of primary and secondary "benign" headaches should be recognised and treated by general practitioner (GPs): a list of signs, symptoms and specific conditions requiring prompt referral from the GP to the neurologist or to the hospital was originally provided by the NMCA in 1994 [8]. Some of these items were then selected and grouped under the heading of "Headache Diagnostic Alarms" (DA), consisting of 7 conditions, each one strongly suggesting the possibility of a secondary headache disorder [9].

The contribution (diagnostic gain) that systematic checking of these items offers has been recently investigated by our group, in a population sample of consecutive cases collected over a 4-week period by neurologists referring to a Regional Headache Network (www.retedeccellenzacefalee.it – Regione Lombardia) [10]. Headache in children and adolescents, major trauma and mass intracranial lesions were considered as exclusion criteria. The distribution of the above 7 DAs among 270 patients attending local EDs was as follows: 8.7% "headache begins after the age of 50"; 30.2% "sudden onset"; 47.4% "accelerating pattern"; 1.1% "new-onset headache in a patient with cancer or HIV"; 5.2% "headache with systemic illness"; 6.6% "focal neurological symptoms or signs other than typical aura"; 0.8% "papilloedema". Association between one or more DAs was found in 39 patients (14.5%). Besides clinical investigations and laboratory tests, the imaging exams performed as first choice were: cranial CT-scan (44%), NMR (19%), cranial or cervical X-ray (3%). At the follow-up visit (7–15 days after ED observation) 85.5% of the cases were definitely diagnosed as primary headaches and 14.5% as secondary forms.

The two most frequent conditions (sudden onset and accelerating pattern) were the only items showing a significant difference among groups (prevalence among primary *vs*. secondary headaches: chi-square test: $p<0.05$). Other possible clinical warning features not included among the above-considered DAs were found in 16 patients (5.9%): unilateral pain; specific precipitating mechanisms; atypical presentation/course, relevant co-morbidities and other pathogenetically related conditions were demonstrated.

A further contribution to the evaluation and management of acute headache in EDs was released by the ACEP in 2002 [11]. This guideline is defined according to the strength of evidence (Class I–III) and classified by level of recommendation (Level A–C).

Among the main statements it is recommended that patients with headache and abnormal findings in a neurological examination should undergo emergent non-contrast CT-scan, the same procedure being recommended for acute sudden-onset headache (Level B).

HIV-positive patients with a new type of headache should be considered for an urgent neuroimaging study (Level B). Cases with a thunderclap headache who have negative findings in both CT-scan and LP (normal opening pressure and negative CSF examination) do not need emergent angiography (Level C).

Abnormal findings in neurological examination in patients older than 50 years with a new type of headache also require an urgent neuroimaging study.

An evidence-based assessment of inpatients' treatment of headache has been recently published reporting the major criteria for patient admission to neurological departments [12].

Comment

A significant amount of the neurological practice within hospitals is dedicated to headache patients with acute disabling symptoms. *De novo* headaches in particular, or a new type of headache, require a careful assessment and a well oriented diagnostic algorithm. Current guidelines and recommendations may help in selecting the appropriate series of diagnostic procedures and the respective time (emergent/urgent). Headache alarms and warnings are also relevant to the clinical practice, but with poor specificity. Available recommendations regarding neuroimaging procedures require continuous updating considering the development of new non-invasive techniques (CT and NMR angiography), which substitute partly but not completely the traditional invasive procedures (cerebral angiography).

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TUTORIAL

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Diagnosing cervicogenic headache

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Abstract The notion that disorders of the cervical spine can cause headache is more than a century old, yet there is still a great deal of debate about cervicogenic headache (CEH) in terms of its underlying mechanisms, its signs and symptoms, and the most appropriate treatments for it. CEH is typically a unilateral headache that can be provoked by neck movement, awkward head positions or pressure on tender points in the neck. The headaches can last hours or days, and the pain is usually described as either dull or piercing. Convergence of the upper cervical roots on the nucleus caudalis of the trigeminal tract is the most commonly accepted neurophysiological explanation for CEH. In most cases, CEH is caused by pathology in the upper aspect of the cervical spine, but the type and exact location of the pathology varies substantially among individual cases. Anaesthetic blocks may be necessary to confirm the diagnosis of CEH, showing that the source of pain is in the neck. Differential diagnosis is sometimes a challenge because CEH can be mistaken for other forms of unilateral headache, especially unilateral migraine without aura. Neuroimaging and kinematic analysis of neck motion may aid in diagnosing difficult CEH.

Keywords Cervicogenic headache • Neck pain • Headache

Clinical picture

Since the first cases of cervicogenic headache (CEH) were identified [1], considerable progress has been made. Particularly in the last decade, there have been advances in therapeutic approach and in defining the clinical picture and diagnostic criteria. As repeatedly stated, CEH is a syndrome, not a disease or an entity *sui generis*. It constitutes a "final common pathway" for pain stemming from several neck disorders. These may involve such structures as nerves, nerve root ganglia, uncovertebral joints, intervertebral disks, facet joints, ligaments, muscles and so on [2, 3]. Pain may accordingly originate at different levels, including the lower part of the cervical spine [4]. CEH comprises all headaches stemming from the neck with the possible exception of specific headache entities (e.g., a subgroup of chronic paroxysmal hemicrania (CPH) with mechanical precipitation of attacks) [3].

CEH has been defined, in principle, as a unilateral headache without sideshift. In the upgrading of the CEH diagnostic criteria [5], the strict unilaterality criterion has

been softened. In clinical practice, patients with bilateral headache may be acceptable (like "the unilaterality on two sides" in tic douloureux) [6, 7]. Because CEH is a syndrome, the pathologic process can, probably not so infrequently, be reproduced on the contralateral side. In these cases, a positive response to appropriate anaesthetic blockades might be essential also in clinical practice (not only in scientific diagnostic work-up), mainly in order to exclude tension-type headache (TTH). Even in the more regular unilateral case, pain may eventually spread to the opposite side when headache becomes severe, while remaining stronger on the original side [5]. The typical unilaterality is probably clearest at attack/exacerbation onset. In CEH, therefore, headache may be strictly unilateral in the most typical and diagnostic case, or it may have a unilateral preponderance; as far as we are concerned, it will not occur solely on the side opposite to the usual one [8].

Other, equally important, diagnostic features are the symptoms and signs of neck involvement. Such signs are mechanical precipitation of attacks (both iatrogenically and subjectively induced), reduced range of motion in the neck – in one or more directions, diffuse ipsilateral neck/shoulder/arm pain of non-radicular nature or, occasionally, arm pain of radicular nature (Table 1). Iatrogenically induced pain similar to the spontaneous one may be elicited by external pressure over tendon insertions in the occipital area. Pressure along the course of the major occipital nerve, over the groove immediately behind the mastoid process, and over the upper part of the sternocleido-mastoid muscle on the symptomatic side may also provoke similar pain. Intrinsic precipitation mechanisms may be activated by neck movements and/or sustained, awkward head positioning during sleep or during wakefulness (such as when washing the ceiling, speaking to one's neighbour at a table during a party, and so forth). Ipsilateral shoulder/arm symptoms may be even more frequent than they seemed to be initially [9]. Not infrequently patients are encountered with marked, more or less constant arm pain of a non-radicular nature [8]. In these cases, the underlying pathology possibly resides in the lower part of the cervical spine (C5 and so on). However, these phenomena are not infrequently of low intensity, and may be more like a discomfort than a pain. Such phenomena may in the occasional case have their own temporal pattern, more or less independent of the headache attacks. The side-locked unilaterality of the headache combined with the ipsilaterality of the arm pain provides rather compelling evidence that headache on such occasions stems from neck structures, but not necessarily only from bony structures.

The duration of attacks/exacerbations varies widely (from a few hours to a few weeks), with a strong tendency toward chronicity; CEH is not infrequently episodic in the initial phase, becoming chronic-fluctuating later on. The pain of attack starts in the neck, eventually spreading to the oculofrontotemporal area, where, during the acme, it may be as strong as or even stronger than in the occipital region [2, 5]. The duration of pain episodes is most frequently longer than in common migraine; the pain intensity is moderate, non-excruciating, unlike cluster headache and usually of a non-throbbing nature.

Table 1 Cervicogenic headache: CEHISG diagnostic criteria [5]

Major criteria	I. Symptoms and signs of neck involvement* Ia. Precipitation of head pain, similar to the usually occurring one: Ia1) by neck movement and/or sustained, awkward head positioning, and/or: Ia2) by external pressure over the upper cervical or occipital region on the symptomatic side. Ib. Restriction of the range of motion (ROM) in the neck. Ic. Ipsilateral neck, shoulder or arm pain of a rather vague, non-radicular nature, or – occasionally – arm pain of a radicular nature. II. Confirmatory evidence by diagnostic anaesthetic blockades. III. Unilaterality of the head pain, without sideshift.
Head pain characteristics	IV. Moderate-severe, non-throbbing pain, usually starting in the neck. Episodes of varying duration, or: fluctuating, continuous pain.
Other characteristics of some importance	V. Only marginal effect or lack of effect of indomethacin. Only marginal effect or lack of effect of ergotamine and sumatriptan. Female sex. Not infrequent occurrence of head or indirect neck trauma by history, usually of more than only medium severity.
Other features of lesser importance	VI. Various attack-related phenomena, only occasionally present, and/or moderately expressed when present: a) nausea, b) phono- and photophobia, c) dizziness, d) ipsilateral "blurred vision", e) difficulties swallowing, f) ipsilateral oedema, mostly in the periocular area.

*It is obligatory that one or more of the phenomena Ia–Ic are present

Autonomic symptoms and signs, like photo- and phonophobia, nausea, vomiting and ipsilateral periocular oedema, are infrequent – and mild if present – and some of them, like vomiting, are clearly less marked than in common migraine [2, 3, 5, 8–10]. In a study by Vingen and Stovner [11], light- and sound-induced discomfort and pain thresholds have been measured in patients with TTH, CEH and in headache-free controls. It is striking that patients with CEH showed a greater photophobia on the symptomatic than on the non-symptomatic side, whereas no such differences were found in TTH and unilateral headaches [11].

Difficulty swallowing is another, rarely occurring, associated phenomenon [1, 4]. There have also been cases with features consistent with a CEH picture, but with additional dizziness and even with vertebral drop-attacks; such patients may benefit from surgical interventions, such as an anterolateral approach toward the cervical spine, *ad modum* Jung. These patients may constitute another clinical subgroup, namely the "vertebral artery type" [8].

Diagnostic criteria

In the revised diagnostic criteria [5] (Table 1), the importance of symptoms and signs of neck involvement has been further stressed. Mechanically precipitated attacks – or pain similar to that of an attack – subjectively and/or iatrogenically induced, is an obligatory requirement for a certain/definite diagnosis, as is the positive anaesthetic blockade effect. Unilaterality without sideshift is highly desirable in scientific works. The lack of Ia criterion will clearly reduce the validity of the diagnosis. It has been proposed that the presence of Ib and Ic, II), and III) criteria, as in the previous version, may be consistent with a "provisional"/tentative diagnosis [5]. In the revised criteria [5], among the "Other characteristics of some importance", the lack of a complete response to indomethacin, sumatriptan and ergotamine has also been introduced. Although CEH is not, in principle, a post-traumatic headache, a history of neck/head trauma should still be considered to be of potentially pathogenetic importance, especially if it is of more than "only medium severity" and has a putative whiplash mechanism [3, 5].

A history of a long-lasting, strictly unilateral headache is suggestive of CEH, in particular if in a female subject. The temporal, that is the "non-clustering", but chronic-fluctuating pattern, and the severity and the non-throbbing nature of the pain (usually moderate and non-excruciating) distinguish CEH from other unilateral headaches, such as cluster headache and CPH. Hemicrania continua (HC) and migraine without aura may represent differential diagnostic problems. An appropriate anamnesis and accurate neurological examination, showing a reduced ROM [12] and precipitation mechanisms, are fundamental elements in distinguishing this headache from others. The combination of pain first felt in the neck and then spreading unilaterally to the frontal area on the same side fortifies the suspicion that one may be faced with a case of CEH. The site and radiation of pain, the temporal pattern and the mechanical precipitation of attacks, both iatrogenically and subjectively, are important aspects of the clinical picture and may help in distinguishing between CEH on the one hand and migraine and TTH on the other [13, 14]. In patients with bilateral pain, but still with a preponderance on the usual side, anaesthetic blockades become mandatory even in clinical practice. In order to single out the correct level of affection, the blockades should be directed to the nerve or nerves where the pain most likely originates/is elicited, on the side of prevailing pain [15].

The IHS diagnostic criteria

In the new IHS classification the criteria for headache associated with neck disorders has been largely revisited (Table 2) [16]. The headache is termed for the first time: "cervicogenic headache" and not "cervical headache".

Table 2 Cervicogenic headache: IHS diagnostic criteria [16]

Diagnostic criteria
A. Pain, referred from a source in the neck and perceived in one or more regions of the head and/or face, fulfilling criteria C and D
B. Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache
C. Evidence that the pain can be attributed to the neck disorder or lesion based on at least 1 of the following: 1. demonstration of clinical signs that implicate a source of pain in the neck 2. abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo or other adequate controls
D. Pain resolves within 3 months after successful treatment of the causative disorder or lesion

However, already under letter "A", it is stated that the pain can be in "…one or more regions of the head and/or face…". In other words, there may be only facial pain and not a headache. Unfortunately, the causes of this headache are only vaguely known, and the finer mechanism largely unidentified. Instead of – under letter "B" – "…known to be or generally accepted as…", this item should probably have been left alone. Fantasy and the creativity of devoted future researchers are relied upon to uncover the causes and not limit them to what is "known". Moreover, it is impossible to decide what is "known/accepted". Another shortcoming of the new classification is under letter "B", where it is stated: "Clinical, laboratory and/or imaging evidence…". As written here, it can be interpreted as meaning: *imaging evidence* would suffice, giving no importance to any headache. Even under letter "C" 1, which suffices for the fulfilment of criterion "C", it is stated: "…pain in the neck" while under letter "D": "pain" is unspecified. Seemingly, a headache does not have to be present.

A minor importance has been deserved the property of CEH to be precipitated. Only in the notes and not in the IHS criteria are the important ipsilateral shoulder/arm symptoms mentioned, which aid in distinguishing CEH from a central affection. These are only some examples of the many shortcomings of these criteria. Unfortunately, these criteria – as the previous ones – may be somewhat unsuited for clinical headache work, and even less so for epidemiological headache work. In retrospect, the 1983 description of CEH may have constituted a ride, a new escalating interest in headache stemming from the neck.

A further refinement of the current diagnostic IHS criteria might make it possible to avoid the existing, partial overlap of CEH and migraine/TTH. We have the feeling that extensive use should be made of the greater occipital nerve – and other blockades – in the routine work-up of CEH, both non-classifiable cases and the mixed forms, in order to improve the efficiency of the current diagnostic system.

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Concepts leading to the definition of the term cervicogenic headache: a historical overview

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Abstract The idea that headache may originate from a problem at the neck or cervical spine level has fascinated and stimulated researchers for centuries. Contributions and reports seeking to clarify this issue have multiplied in the past 80 or 90 years. Bärtschi-Rochaix reported what seems to have been the first clinical description of cervicogenic headache, but it was not until 1983 that Sjaastad and his school defined diagnostic criteria for this sydrome. The current, revised International Headache Society Classification (ICHD-II) includes the term cervicogenic headache, but the diagnostic criteria it gives differ from those of the International Association for the Study of Pain (IASP), and also from the most recent Cervicogenic Headache International Study Group (CHISG) definition (1998).

Keywords Cervicogenic headache • History of headache • Cervical spine • Anaesthetic blockade

Introduction

The term cervicogenic headache (CEH) refers to a head pain condition that has its origin in the neck. Such ideas – headache of nuchal origin – must have occupied the minds of men for centuries. A more systematic search for such headaches seems to have been made only from the early stages of last century [1]. The reason for the lack of breakthrough of such ideas was probably the vague, indistinct descriptions of the headache in the original works, and confusion with other headaches, like migraine without aura and tension-type headache, none of which were properly defined at that time. Cardinal symptoms, beside the headache, were supposed to be dizziness, visual disturbances and tinnitus – the attacks in part lasting two to three hours. This constellation of symptoms has little to do with the CEH picture that we know today. Clinicians who conscientiously were searching for cases of headache stemming from the neck on those premises could be easily and widely misled. An overview of the early description could be the basis for a better understanding of the current terminology as far as CEH is concerned.

The early descriptions

Bärtschi-Rochaix [1] maintained that the first clinical description of a headache linked to a problem in the neck was published by Schützenberger, in 1853. Unfortunately, this description is not available in the literature. In a 1913 report – this is the first clinically significant one that we are able to access – Holmes [2] claimed that headache could originate from the neck. This author described headaches associated with the presence of painful nodules in the posterior muscles of the neck, which he attributed to fibrositis. This provided the basis for the subsequent definition of "rheumatic headache", which was described by others writing at this time [3, 4].

Barré, in 1926 (and possibly even a year earlier) [5], described a headache with greater intensity in the occipital region, associated with dizziness and with hearing and visual disturbances, and called this picture "posterior cervical sympathetic syndrome". In 1928, Lieou [6] added "pain referred to the larynx and pharynx".

In 1940, Haddon [7] described a clinical picture characterised by unilateral pressing pain, starting in the suboccipital region and radiating anteriorly to the temporal and often also to the retro-orbital region unilaterally. This clinical picture was sometimes associated with photophobia and, in severe cases, pallor, profuse sweating, hyperaesthesia in the nerve distribution area and, on occasions, also with vomiting. During an attack, the application of pressure to the greater occipital nerve (GON) or the small occipital nerve could accentuate the pain. Haddon called this pain "occipital neuralgia" and recommended, for its treatment, injections of procaine hydrochloride or alcohol at the site of the hyperaesthesia. Over the following years, there were other reports of headache possibly related to the neck, but the clinical descriptions given were less precise [8, 9]. It was to be a few more years before reports appeared that led to the inclusion, in the sphere of headache originating from the neck, of cases in which the pain was induced by the stimulation of trigger points ("mechanical headache") [10, 11].

It is worth mentioning the important studies conducted by Ray and Wolff [12]. These authors showed that stimulation of the sensory nerve endings above or below the upper surface of the tentorium cerebelli produced head pain that could be felt centrally (at the vertex) and frontally. Over the next few years, the afferent connections of the upper cervical nerves were also investigated [13]. In 1949, Hunter and Mayfield [14] made a major contribution to clarifying and developing the concept of CEH, describing 11 patients presenting with recurrent attacks of severe migraine-like pain which, at its height, could become holocranial; the pain started in the suboccipital region but radiated to the vertex, to the temporal region and to the periorbital region, often bilaterally. The attacks would be accompanied by symptoms such as lacrimation, facial flushing, profuse sweating and, on occasions, nasal congestion on the more severely affected side. In a high percentage of cases, the patients had sustained a direct trauma to the neck. The clinical picture also included (in just a few patients) postural instability and dizziness, and a couple of patients also complained of vomiting during particularly severe attacks. This pain could be interrupted by anaesthetic blockade of C_2. Blockade of the GON also modified the pain of an attack, but less rapidly and less completely. The patients described in this report underwent avulsion of the GON, either with intraspinal section of the sensory root of C_2, or with intraspinal sections of the sensory roots of C_2 and C_3. Raney and Raney [15], meanwhile, investigated the intervertebral cervical disc as a possible trigger factor for headache.

The next important contribution was Bärtschi-Rochaix's 1949 monograph on "cervical migraine" [16]. Practically all the patients described (32 out of 33) had headache or "paraesthesia of the head". The pain would start at the back of the head and extend to the central, parietal or frontal regions. All the patients but one showed signs and symptoms linked to the neck, mainly nuchal pain on the same side as the headache, and many of them had reduced mobility of the cervical spine. Four patients had a history of drop attacks. Around half the patients suffered brief scintillating scotoma episodes (n=10) or visual fogging (n=5) coinciding with the headache attack. In a high number of cases (n=18) the pain/paraesthesia – mainly pain but sometimes paraesthesia (n=6) – spread to the upper extremities, usually unilaterally, but occasionally bilaterally. This description was the first to include the finding of headache following cervical trauma [11], and in his 1968 series Bärtschi-Rochaix [1] also included patients with degenerative alterations at the cervical level. He described radiological alterations in the uncovertebral facet joints at levels C_3-C_4, C_4-C_5, C_5-C_6 and C_6-C_7, the most characteristic being those at levels C_3-C_4 and C_5-C_6. The author called these radiological findings "casseroles entassées" and "assiettes empilées"; the first of these expressions described exostoses of the uncovertebral joints of both distal and proximal vertebra, whereas in the second case only distal exostoses (affecting the uncinate process) were clearly visible. The patients studied presented morphological alterations of the uncovertebral facet joints and Bärtschi-Rochaix divided these alterations into four stages. The author used the term "cervical migraine" because he considered this migraine-like picture (unlike classic or "carotid" migraine) to be attributable to an alteration of the posterior circle.

The surgical evidence and the blockade effect

Cloward [17] studied projection of pain following stimulation of the anterior and anterolateral part of the disc during 114 cervical discographies. Pain following stimulation of C_3-C_4 was referred to the scapular region, whereas stimulation of C_4-C_5, C_5-C_6 and C_6-C_7 produced pain at the superior-medial, medial and inferior border of the homolateral scapula. Stimulation at the level of the median line, anteriorly, induced pain in the middle part of the thoracic area. Most of the patients perceived pain referred from the posterior surface of the lower cervical discs in one or more of the following areas: (1) the upper part of the scapula, (2) the base of the neck, (3) the upper part of the shoulders, (4) the inferior border of the scapulae, (5) the upper arm, radiating down as far as the elbow. This last point is particularly interesting, as pain radiating to this area is one of the characteristics of CEH.

Pentecost and Adriani [18] described the effects of cervical blockade in patients presenting with unilateral headache, with pain starting in the suboccipital region and radiating upwards to the occiput of the cranium. The authors submitted 63 patients to anaesthetic blockades of C_2 and C_3. Six patients did not derive any benefit; in 10 the pain improved partially; and in the remaining patients the pain was, temporarily, eliminated completely. In some patients, GON and small occipital nerve blockades were tried as an alternative, but these produced only partial resolution of the pain.

The anatomical basis

Kerr and Olafson [19] demonstrated, in the cat, convergence of trigeminal and cervical afferents in the intermedial and ventral dorsal horn at the level of the upper cervical cord. On the basis of this anatomical pathway it is possible to hypothesise a spreading of the hemicranial pain from cervical to trigeminal areas. According to these authors, this convergence could also explain a reflex pathway, probably related to head turning in response to trigeminal stimuli. Kerr [19–21] believed that atypical facial neuralgias [19] and other facial and cranial pain syndromes could be explained on this basis. These authors then described a recurrent clinical picture characterised by severe, periodic headache, aggravated by head and neck movements. Typically, these patients presented pain that began with a deep sensation of pressure in the suboccipital region unilaterally, which could extend to the occipital, parietal and fronto-orbital regions and down to the shoulder and arm; sometimes, it could even radiate to the mandibular and maxillary regions.

Kehr et al. [22] described two surgical methods: uncosectomy and uncoforaminotomy according to Jung (anterolateral approach), indicated in cases of "cervicocephalic syndrome, Barré-Lieou syndrome and cervicobrachial syndrome". The first of these three syndromes included, in addition to the headache: cochlear, vestibular and ocular symptoms, a sensation of postural instability, lower limb weakness, or drop attacks, and psychological symptoms, such as generalised weakness and depression. The symptoms occurred episodically and were triggered or worsened by neck movements, particularly rotation and extension. Pasztor [23] emphasised the need, in these cases, to remove any fibrotic tissue around the vertebral artery.

Knox and Mustonen [24], investigating a sample of 30 patients (27 women and three men, aged 17–72 years), described greater occipital neuralgia as an ocular pain syndrome in which the eye, the eye socket and the temple could be affected; hyperaesthesia was found on application of pressure to one or both the occipital nerves, and the authors considered this a key criterion for diagnosis. The therapy proposed was local injection of an anaesthetic drug into the most affected area.

Chouret [25] affirmed that "greater occipital neuralgia headache" had an occipital, temporal and frontal distribution and was usually bilateral. The pain was described as dull and constant.

Definition of occipital neuralgia, on the other hand, proved more problematical. According to the most widely accepted description, it is a stabbing pain in the nerve distribution area, similar to that of trigeminal neuralgia.

As we have shown, the literature reports many cases of headache that can be linked to cervical spine disorders, even though the majority of these, because of a lack of evidence, had fallen into oblivion. The various descriptions that, over the decades, have appeared in the literature present very diverse features, even though, in retrospect, it may seem that they also have many features in common. In general, it can be remarked that even though the idea that headache can be related to disorders of the neck is accepted to differing degrees by the different schools of thought, there is still no consensus on the question of whether the neck can play a key role in the genesis of a headache. Up until the start of the 1980s, headache originating from the neck had no place in the International Headache Classification [26].

The term "cervicogenic headache"

The term cervicogenic headache was introduced by Sjaastad and co-workers in an article published in 1983 [27]. The first description of CEH was greeted somewhat sceptically in scientific circles. In the years that followed, there continued to be considerable opposition to these clinical criteria and headache scientists only gradually came to accept the con-

cept. This real reluctance – even after Sjaastad's 1983 contribution – to entertain the idea that headache can derive from the neck probably constitutes the best evidence that the problem had not, until that point, been properly tackled. The whole CEH story – and unfortunately it is not the only one of its kind in the history of medicine – reveals the conservative outlook of the medical community and its unwillingness to embrace new theories, even when these are based on logical arguments and supported by evidence. The term cervicogenic headache by definition describes an out-and-out headache in which there is clear involvement of the neck and possibly a neck-related aetiopathogenesis: "cervicogenic" meaning that which originates in the neck. From this perspective, the term "cervical" is misleading, while "cervical headache" is a contradiction in terms. Nevertheless, this was the term used in the diagnostic criteria published by the International Headache Society (IHS) in 1988 [28].

A crucial step in the evaluation of these nosographic aspects came in 1987 when Ottar Sjaastad, in Florence, set up the Cervicogenic Headache International Study Group (CHISG). This group has met annually ever since. Its diagnostic criteria were first published in 1990 [29] and revised in 1998 [30].

International coding of cervicogenic headache

The International Association for the Study of Pain [30] accepted cervicogenic headache a decade ago as a distinct headache syndrome, utilising principally the Sjaastad criteria [31].

The IHS recently published a new version of its classification [32] in which the term cervicogenic headache appears, but with diagnostic criteria different from those of the CHISG. Moreover, the present criteria, as the previous in 1988, may be somewhat unsuited for clinical headache work. In the IHS criteria the pain location is not properly specified, the causes of pain are only vaguely known, neuroimaging would suffice for diagnosis, there is no mention of precipitability of pain and, last but not least, the ipsilateral shoulder/arm symptom radiation is not reported.

The definition of "cervicogenic headache" marked a turning point. Indeed, the state of our knowledge now is entirely different from what it was when this term was first introduced. Since that time, many cases of CEH have been reported and in many scientific circles the definition and the diagnostic criteria are rapidly gaining ground, and support for these nosographic criteria is increasing almost exponentially. Nevertheless, the fact remains that neither the term nor the concept are yet accepted by the entire scientific community. One major obstacle to full acceptance of CEH as a separate entity is the fact that both the definition and the diagnostic criteria are regarded as "homespun". We believe that the current nosographic criteria, established by the CHISG, constitute an important starting point for conducting clinical studies in large series of patients and for a rigorous assessment of the whole question of CEH.

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Guidelines for the organization of headache education in Europe: the headache school

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Summary

According to its mission statement, one of the goals of the European Headache Federation (EHF) is to "educate Europe" about headache through the teaching of the key health personnel, such as young physicians and all those involved in headache management, about the seriousness of headache disorders.
The countries of Europe share a close geographical proximity that facilitates international exchanges, particularly between university faculties. In recent years, this has, indeed, been the working basis of European educational endeavours in the field of headache. For a number of years, annual summer schools were organized in different European countries and a permanent Summer Headache School was set up in Cambridge (to be held every alternate year). The last summer headache school was held in Vilnius in 2002. In the past decade, a patronage scheme was also set up, which, combining two or more countries (one developed, one or more developing), allowed international exchanges of doctors and students for training purposes. In some centres, participants were also able to gain clinical practice and research experience by staying at the host institutions for extended periods of time.
As a result of all this activity there have emerged, in Europe, "clusters" of people with a particular interest in headache. However, the rapid growth of insight into headache (new molecules, new headache categories, etc.) has contributed to a widening of the scientific gap between developing and developed countries. Moreover, in the past four years, due to the relative restriction of national/international drug company budgets, it has proved possible to organize only relatively inexpensive teaching courses. As a result, countries whose medical communities had been developing a "headache culture" now find themselves destined to be increasingly held back.
Therefore, the EHF, in order to promote education on headache in Europe at national level, felt there was a need for guidelines for the organization of educational courses that meet uniform standards of excellence and in terms of code of conduct: guaranteed courses that will attract investors and those seeking to increase their knowledge, skills and understanding in the area of primary and secondary headache.
The guidelines, presented here, specify the ideal length of a headache course, the number of lectures it should include, as well as the ideal number of participants and teachers. A sample course outline is provided, together with a checklist to help the organizers to meet the criteria for an EHF-approved headache school.

KEY WORDS: education, Europe, headache.

Introduction

According to its mission statement, one of the aims of the European Headache Federation (EHF) is to "educate Europe" about headache (1). This can probably best be done by teaching key health personnel, such as young physicians and those involved in the management of headache patients, about the various headache forms and in particular about the serious forms of headache.
The countries of Europe are in close geographical proximity to one another and this proximity favours international exchanges, particularly between university faculties. In recent years, this has, indeed, been the working basis and successful mechanism of European educational endeavours in the field of headache. Beginning in 1992, a summer school was, for several years, held annually in different European countries: Antalya, Stresa, Oporto, Cambridge, Copenhagen, Kiel. Then, Cambridge

became the venue for a permanent Summer Headache School (to be held every alternate year); the last summer headache school was held in 2002 in Vilnius.
In the past decade, a patronage scheme was also set up, which, combining two or more countries (one developed, one or more developing), allowed international exchanges of doctors and students for training purposes. The countries participating in this successful scheme were: Albania, Austria, Bulgaria, Croatia, Italy, Lithuania, Norway, Russia, Slovakia, Slovenia (1,2). In some centres, participants were also given the opportunity to gain clinical practice and research experience by staying at the host institutions for extended periods of time, and this allowed them to achieve a higher standard of training (2,3). As a result of all this activity there have emerged, in Europe, "clusters" of people with a particular interest in headache.
The EHF has also put a lot of effort into producing easy reading booklets on the basic concepts of primary headache, targeting general physicians (3-5).
However, the rapid growth of insight into headache (new molecules, new headache categories, etc.) has contributed to a widening of the scientific gap between developing and developed countries. Moreover, in the past four years, due to the relative restriction of national/international drug company budgets, it has proved possible to organize only relatively inexpensive teaching courses (e.g., Lithuania in 2002).
As a result, countries whose medical communities had been developing a "headache culture" now find themselves destined to be increasingly held back. In view of all these considerations, it was deemed useful, in order to promote education on headache in Europe at national level, to develop guidelines for the organization of educational courses that meet uniform standards of excellence and in terms of code of conduct – in short, guaranteed courses that will attract investors and those seeking to increase their knowledge in this field.
A sample course outline, developed in accordance with the systematic guidelines presented in this paper, is given below (see Appendix).

Teaching course format

Target of the guidelines

These guidelines are aimed at institutions, such as national neurological societies, European neurological societies or allied scientific organizations, that are planning to organize headache teaching courses at postgraduate level.

Aim of the course

The aim of the course is to enable participants to gain knowledge, skills, and understanding, in the area of primary and secondary headache, that will contribute to their personal and professional development. By the end of the course, they should have enhanced their clinical skills, including their capacity to interact appropriately with affected individuals. Ideally, this should translate into an enhanced quality of life for headache sufferers.
The key aim is that the knowledge gained from the course be applied in the participants' various professional fields. The national society/research group hosting the course will apply to the appropriate authorities for Continuous Medical Education (CME) credits. In this way, the participants will be attending a course that can contribute to a certified university qualification.
The target audience may include general practitioners, general neurologists, clinical pharmacologists, and internal medicine specialists, and the course brochure should specify which of these it is aimed at, and be planned accordingly.
The teaching course must be specifically designed to help participants to:
– recognize the various clinical presentations of headache;
– become familiar with the "red flags" and "comfort signs" approach to diagnosing secondary headaches;
– understand the latest concepts in headache pathophysiology;
– develop treatment plans for helping patients with all aspects of their headache treatment needs;
– formulate a headache management "toolbox" for patients, incorporating acute and preventive treatment approaches;
– devise strategies in order to help patients understand headache treatment tactics and improve patient compliance with therapeutic plans.

Topics

Each day of the course, which should cover both primary and secondary headaches, must incorporate both theory and practical teaching.
The organizers should ensure that any slides used are kept as concise as possible, given that it takes at least 40-60 seconds to explain and understand a slide. Speakers must submit their slides in plenty of time so that they can be printed and available for distribution, on a daily basis, during the course.
Video recordings are the best medium for presenting illustrated case reports on both simple and complex cases, and for making sure that the participants retain the information given. Ten minutes video plus 10-15 minutes' discussion time are usually enough to become familiar with a clinical history. At least two videos per day should be included in the programme.

Venue

The course should preferably be organized in a hospital/university setting. Expensive hotels with tourist facilities should be avoided.

Duration of the course

The ideal/minimum duration of a course is three days. Concise one-day courses can be organized under the supervision, or with the advice of the EHF, on condition that the recommended ratio of practical/theoretical teaching is respected.

Number of participants and structure of lectures

Overcrowded courses prevent the participants from interacting with the lecturers and clearly lower the general level of attention. Around fifty participants should be admit-

ted, ideally divided into two parallel sections of 25 each. The attention of the participants is negatively correlated with the length of the lecture. On the basis of prevailing experience, a duration of 20-25 minutes (+ 5 minutes for questions) is recommended. The course programme should schedule 7-8 teaching hours per day (approximately 15 lectures/case reports). A key element in courses of this kind is the panel discussion or discussion group, which should never be missing from the programme.

Teaching staff

The course should provide participants with an opportunity to share in the experience of international scientists and to exchange opinions and ideas. A 3-4 day course should have a teaching staff of 3-5 foreign lecturers (finances permitting), who should each be given the opportunity to give at least two lectures. The remaining lectures will be given by the local organizers. The discussion at the end of each lecture or at the end of a session gives all the participants an opportunity to express their ideas, considerations, second thoughts, etc. Therefore, each session should have at least two chairmen, whose role is to raise controversial issues and questions, requesting the speaker to express his own personal opinion, or international opinion, on certain topics.

Official language

The official language of the course should possibly be English; in certain situations, national languages can be used, provided that students or doctors are offered translation. Lectures should be given with the aid of telematic means (Powerpoint or similar).

Teaching material

Slide handouts should be available at the beginning of the course. The course material should also include a brief curriculum vitae of each lecturer. The EHF's own congress organizer can help in the assembling of the teaching material.

Evaluation test

A multiple choice questionnaire should be filled in by each participant at the beginning and at the end of the course. The evaluation test should include two questions relating to each lecture. The test results will be mailed to the participants after the course. The EHF may provide an evaluation questionnaire if requested by the organizers. In order to gain CME credits, the participant should attend 80% of the scheduled activity. Vice versa, the participants will also be asked to give their evaluation of the speakers and lecturers.

Miscellaneous

The course format should be included in the preliminary and final programme brochure.
In order to be formally approved by the EHF, the course format should be mailed to the President of the European Headache Federation who will distribute the application to the federation's board members for approval. The EHF may offer financial support to countries with limited local funding (e.g., covering economy flights for 3-5 foreign speakers).
The local organizing committee and the course chairman are responsible for promoting and marketing the course locally. The EHF's own congress organizer may help the local congress company with logistical organization.
The EHF can, upon request, provide the following material.
– IHS Classification slide kit;
– Evaluation test;
– Standard three-day programme (see Appendix) or personalized programme;
– Currently available teaching materials (booklets, brochures, etc.).

Concluding remarks

Teaching is an essential part of academic headache specialty practice and represents a major task for international societies (7). According to a survey in the USA (8,9), 22% of medical schools do not run lectures on headache, and 43% of postgraduate programmes did not include resident lectures on headache. It goes without saying that it takes both time and energy to devise an optimal teaching strategy for the training of new generations of headache specialists. However, one of the priorities of the EHF is to upgrade the level of awareness of and insight into headache problems. Therefore, to achieve systematic education in headache research and clinical practice, there has to be comprehensive teaching. We have a strong feeling that the availability of a proposed headache course format might facilitate the spread of knowledge and understanding of headache in European countries.

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Appendix

Checklist of European Headache Federation requirements for the organization of a teaching course on headache

☐	Title of the teaching course: Date: City:
☐	Chairman of the scientific committee: Institution: E-mail/fax:
☐	Congress venue:
☐	Number of participants: Parallel sections:
☐	Number of foreign lecturers:
☐	Duration of the course:
☐	Duration of the lectures:
☐	Daily practical/theoretical teaching:
☐	Telematic media:
☐	Multiple choice evaluation test:
☐	Handout material requested:
☐	Official language:
☐	Guidelines provided with course material:
☐	Preliminary programme submitted:
Notes	

Sample format of a three-day headache course:

LOCAL ORGANIZATION FOR THE STUDY OF HEADACHE

in conjunction with

EUROPEAN HEADACHE FEDERATION

presents

Title of the course

International School on Headache and Related Disorders
Venue, City

Day 1-3 Month, Year

DAY 1, *DATE*

8.30-10.30 **section 1**
Chairmen:
8.30 Special Lecture 1: **Classification of Headache** (speaker, 30 min.)
9.00 Epidemiology of headache (speaker 20-25 min., discussion 5 min.)
9.30 Pathophysiology of headache
10.00 The burden of headache
10.30-11.00 *coffee break*

11.00-13.00 **section 2: Migraine**
Chairmen:
11.00 Classification of migraine
11.30 Clinical picture of migraine
12.00 Complications of migraine
12.30 Taking the headache history
13.00-14.00 *lunch*

14.30-16.30 **section 3: Migraine**
Chairmen:
14.30 (video) case report
15.00 Comorbidities of migraine
15.30 Acute drug treatment: NSAIDs & ergotamine
16.00 Acute drug treatment: triptans
16.30-17.00 *coffee break*

17.00-18.30 **section 4: Migraine**
Chairmen:
17.00 (video) case report
17.30 Prophylactic drug treatment: part 1
18.00 Prophylactic drug treatment: part 2
20.00 *dinner*

DAY 2, *DATE*

8.30-10.30 **section 1: Tension-type headache (TTH)**
Chairmen:
8.30 Special Lecture 2: **Pathogenesis** (speaker, 30 min.)
9.00 Epidemiology of TTH (speaker 20-25 min., discussion 5 min.)
9.30 Classification and clinical picture
10.00 Comorbidities of TTH
10.30-11.00 *coffee break*

11.00-13.00 **section 2: Tension-type headache**
Chairmen:
11.00 Pharmacological treatment
11.30 Non-pharmacological treatment
12.00 Temporomandibular dysfunction and headache
12.30 Medication-overuse headache
13.00-14.00 *lunch*

14.30-16.30 **section 3: Various**
Chairmen:
14.30 (video) case report
15.00 Other primary headaches
15.30 Cervicogenic headache
16.00 Headache in the emergency department
16.30-17.00 *coffee break*

17.00-18.30 **section 4: Various**
Chairmen:
17.00 (video) case report
17.30 Cranial neuralgias
18.00 Which examinations in headache?
20.00 *dinner*

DAY 3, *DATE*

8.30-10.30 **section 1: Trigeminal autonomic cephalalgias (TACs)**
Chairmen:
8.30 Special Lecture 3: **Pathogenesis of TACs** (speaker, 30 min.)
9.00 Epidemiology and classification of cluster headache (speaker 20-25 min., discussion 5 min.)
9.30 Clinical picture
10.00 Pharmacological treatment
10.30-11.00 *coffee break*

11.00-13.00 **section 2**
Chairmen:
11.00 Paroxysmal hemicrania: clinical picture and treatment
11.30 SUNCT
12.00 Differential diagnosis of TACs
12.30 Post-traumatic headache
13.00-14.00 *lunch*

14.30-16.30 **section 3: Various**
Chairmen:
14.30 (video) case report
15.00 Headache in the elderly
15.30 Headache and reproductive life
16.00 Treatment of menstrual migraine
16.30-17.00 *coffee break*

17.00-18.30 **section 4: Headache in children**
Chairmen:
17.00 (video) case report
17.30 Migraine in children
18.00 Use of drugs in children
20.00 *dinner*

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Single high-dose steroid treatment in episodic cluster headache

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Cephalalgia

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Corticosteroids appear to be the most rapid-acting of the prophylactic drugs used in the treatment of cluster headache (CH). These agents are frequently employed as a short-term regimen to induce clinical remission. In this study, we assessed in an open fashion the effect of high dose methylprednisolone (MPD) in a group of 13 patients with episodic CH (3 females and 10 males). On the 8th day of the active period, MPD was administered intravenously at the dose of 30 mg/kg body weight, as a 3-h infusion in saline. The attack frequency was followed for 7 days. The mean daily attack frequency before MPD administration was statistically different from that reported after treatment (respectively: 1.38 ± 0.42 and 0.83 ± 0.78; $P = 0.05$ Student's t-test). The mean interval between MPD administration and the occurrence of the first subsequent attack was 3.8 ± 2.2 days (range: 2–7 days). Only 3 (23%) of 13 patients experienced a complete headache remission. No significant side-effects were noted after MPD administration. These data further demonstrate that in most patients with episodic CH, high-dose systemic steroid administration may invariably interrupt attack recurrence for a few days, but is ineffective in maintaining complete clinical remission. This study also suggests that MPD administered as a solitary dose does not provide any advantage above prednisone in CH treatment. □*Cluster headache, steroid therapy, symptomatic treatment, transitional prophylaxis*

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Introduction

Several drugs are commonly used in the short-lasting prophylactic treatment of episodic cluster headache (CH). The main aim of such an approach is to obtain a prompt interruption of the series of pain attacks. If this is not achieved, one can at least obtain a decrease in frequency, duration, and intensity of CH attacks. A secondary aim is to maintain remission for a period longer than that expected in the absence of treatment.

Among the prophylactic agents used in CH, corticosteroids, such as prednisone and dexamethasone, are the most rapid-acting ones (1). Due to their rapid setting-in efficacy and their potency, they are generally most useful during the time necessary for other prophylactic drugs to be started and become effective. There is clinical evidence at hand concerning the effectiveness of corticosteroids in CH, even though it mostly derives from studies performed according to uncontrolled experimental designs. The largest series ($n = 77$) is that by Kudrow (1), that showed that 60 mg prednisone was completely effective in inducing a persistent remission, in 77% and partially effective in another 12% of episodic CH patients. This efficacy appears to be strictly dose-dependent. Dexamethasone, at the dose of 4 mg b.i.d. for two weeks followed by 4 mg/day for one week, has also been shown to be beneficial (2).

Recently, a treatment with methylprednisolone (MPD) i.v. followed by prednisone orally has been

reported to be more effective than the usual prophylactic treatment (3).

Uncertainty exists as to the effectiveness of steroids in inducing a stable clinical remission. Several observations (4–6) as well as scattered clinical experience suggest that once the doses of dexamethasone or prednisone are tapered, pain attacks almost invariably tend to recur, and additional therapy must be given. This tendency probably depends upon dosage and duration of therapy (4). On the other hand, a steroid treatment course extended beyond a three week period may not be well tolerated by all patients.

Over the past years, it has become widely accepted that the use of high-dose steroids, such as MPD 0.5–1 g/day intravenously for a period of 3–10 days, is effective in various neurological diseases (i.e. demyelinating diseases, such as multiple sclerosis) and other immune disorders. In these cases, steroids have generally been found to be well tolerated, more effective than when administered at lower doses for longer periods, and devoid of major adverse effects. With this in mind, a study with a different design was carried out by Cianchetti et al. (7), who placed a single CH patient on a regimen of repeated administration of MPD 0.5–1 g/day i.v., and found a beneficial effect, lasting 4–5 days on each occasion.

The aim of the present study was therefore to evaluate in a sizeable group of episodic CH the effectiveness of a single, high-dose, parenteral steroid administration in inducing and maintaining a relative long clinical remission.

Materials and methods

Patients

The study group consisted of 13 patients, 3 females and 10 males, aged 48 ± 10 years (mean ± SD), with CH in active phase; the patients were enrolled consecutively. CH was diagnosed according to the International Headache Society (IHS) criteria (8). The study was carried out at an outpatient clinic basis. Patients were not suffering from uncontrolled hypertension, diabetes, peptic ulcer or diabetes mellitus. After obtaining informed consent from all patients, a complete clinical history was taken before the actual bout. Patients were instructed to record attacks using a dedicated headache diary, starting from day one of a new cluster period, and then to contact investigators and appear at the out-patient clinic on day eight. After the seven day run-in period, the steroid was invariably administered on day eight. At the end of the day of drug administration, the patients were dismissed and instructed to continue to fill in the headache diary and to contact medical personnel in case of recurrence, or in any case after 3–5 weeks, to report on the state of their headache.

The frequency of the pain attacks, the cluster period duration, as well as other individual, clinical features of the patients studied are reported in detail in Table 1. At the time of testing, patients were having regular headache attacks, and none of them had taken any prophylactic medication since the beginning of the period. For ethical reasons, patients were allowed to use sumatriptan 6 mg s.c. as acute treatment whenever required, both in the run-in period and for breakthrough attacks during the study. In case of headache recurrence after MPD, the patients would be given prophylactic treatment within two days of recurrence of attacks.

Procedures

A scheme of the study design is shown in Fig. 1. Before MPD administration, routine blood tests and ECG were taken. The treatment was always carried

Table 1 Clinical features (of CH patients) before and after methylprednisolone (MPD) infusion. Values are expressed as mean ± SD

	Before MPD	After MPD
Cluster period duration in all patients (days) ($n = 13$)†	35 ± 12	27 ± 19
Cluster period duration in patients with recurrence after MPD (days) ($n = 10$) † §	36 ± 12	35 ± 13
Attack frequency/24 h in all patients ($n = 13$)	1.38 ± 0.42	0.83 ± 0.78*
(range)	(1–3)	(0–4)
Attack frequency/24 h in patients with recurrence after MPD ($n = 10$) § (range)	1.46 ± 0.46	1.08 ± 0.72
	(1–3)	(0–4)
Interval between MPD administration and first subsequent attack ($n = 10$) (days and range)	–	3.8 ± 2.2
		(2–7)

*$P = 0.05$ vs. prior to MPD (Student's t-test); † present vs. latest cluster period; § same group of patients.

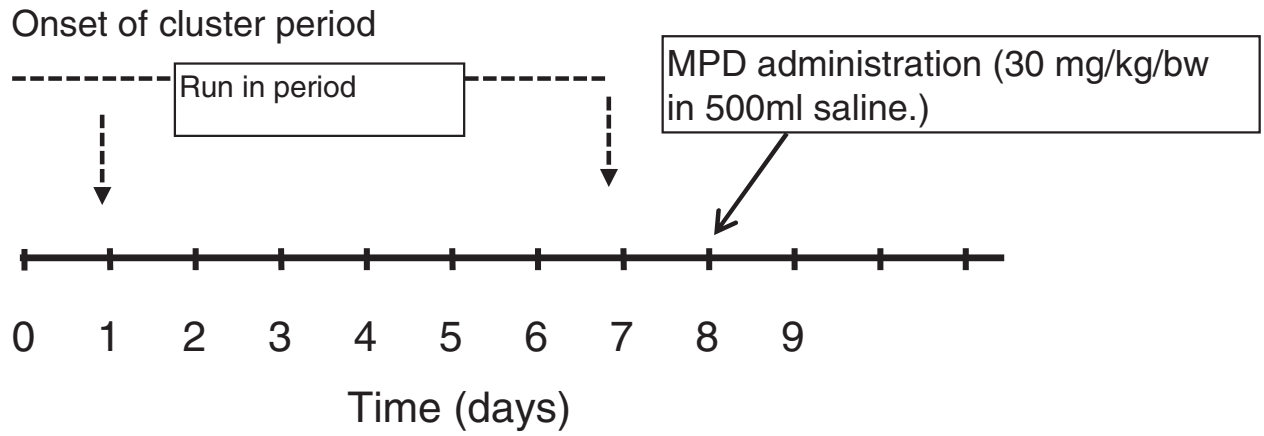

Figure 1 Schematic illustration of the temporal relationship between the onset of the cluster period and methylprednisolone (MPD) treatment.

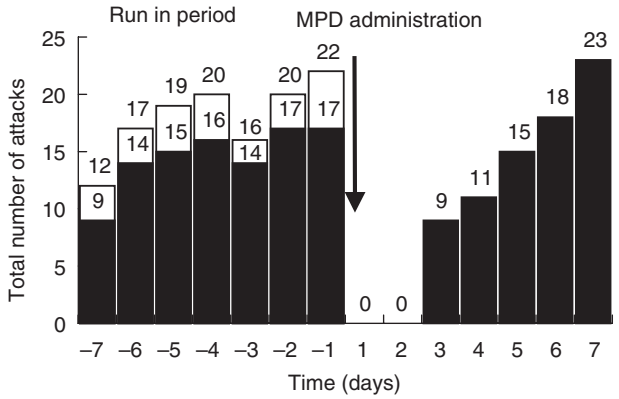

Figure 2 Daily number of attacks on each day from the onset of the cluster period, during methylprednisolone (MPD) treatment, and afterwards. Data refer to patients with recurrence of attacks. ■ patients with recurrence of attacks ($n = 10$); ■+□ total number of patients ($n = 13$).

out on the 8th day of the active phase. MPD 30 mg/kg body weight in 500 ml saline, was administered as a 3-h infusion, starting at 9.00 a.m.

In order to assess the MPD response, the following parameters were evaluated (1): the mean daily attack frequency over 7 consecutive days prior to MPD and during the 7 days following treatment (2); the mean interval and range between MPD and the occurrence of the first, subsequent attack.

The mean daily attack frequency during the observation period in patients with headache recurrence after MPD is shown in Fig. 2.

Statistical analysis

Normal distribution of clinical data was found with the Kolmogorov-Smirnov test. For the comparison of attack parameters before and after MPD treatment, statistical analysis was carried out, using paired *t*-test, the only exception being when comparing pain free days, in which case the Wilcoxon test was used. Differences were considered significant if $P < 0.05$. Data are expressed as mean ± SD.

Results

No major side-effects were noted after MPD administration. In all cases, attacks were discontinued after MPD and did not reappear for two or more days. The mean duration of the previous cluster period in each of our patients was found to be 36 ± 12 days (based on their diary cards), while the mean duration of the actual period, with MPD, was 27 ± 19 days. As shown in Table 1, there was a significant difference between the mean frequency of daily attacks during the 7 days preceding MPD administration and the 7-day period following treatment ($n = 13$; 1.38 ± 0.42 and 0.83 ± 0.78, respectively; $P = 0.05$ Student's *t*-test). However, there was no significant difference when considering only patients with recurrence of attacks after MPD ($n = 10$; 1.46 ± 0.46 and 1.08 ± 0.72, respectively; $P = 0.23$ Student's *t*-test). The total number of attacks was 126 ($n = 102$ if patients with no recurrence were excluded) before and 76 after MPD. CH attacks did not occur during the infusion, with the exception of one patient who experienced typical signs and symptoms 1.5 h after the beginning of the infusion. The mean number of pain-free days before MPD was 0.2 ± 0.4, while after MPD it was 3.9 ± 2.2 ($P < 0.005$, Wilcoxon test).

The mean interval between MPD administration and the occurrence of the first subsequent attack was

3.8 ± 2.2 days (range: 2–7 days) (Fig. 2). These results concern 10 cases, since 3 of the 13 patients (23%) did not experience any attack recurrence after MPD treatment. The clinical features (i.e. headache frequency, period duration, etc.) in two of the patients did not show peculiar aspects when compared to those of the patients with a recurrence after MPD However, one patient without recurrence had a previous period duration of two weeks. Three patients with attack recurrence 7 days after MPD injection were followed up to 10 days to ascertain the temporal pattern. The recurrence of attacks after MPD is reported in Fig. 3.

Discussion

The beginning of the active period is likely to be the most suitable period for evaluating the efficacy of a given drug in CH. Indeed, the chances of a spontaneous recovery increase with the advancement of the bout, so that in the medium-late phase of the CH period the observations made on the effects of a given agent become unreliable. Accordingly, in our study we chose the very onset of a cluster period (from day 8 onwards) to test the effect of MPD in a selected group of patients with a well-established headache pattern. By using the experimental design described above, it would conceivably be possible to reach a clear-cut conclusion on any protective effect of parenteral MPD and on the temporal aspects.

In our study, 77% of CH patients (10 out of 13, in the active phase) showed a stereotyped response, i.e. cessation of attacks for 2 or more days following the treatment. The mean duration of the pain-free period was of the same order of magnitude as that observed by others in a previous study (7). However, the spectrum of the response was much wider when more patients were included. In addition, the patients with no recurrence did not show peculiar features of their headache.

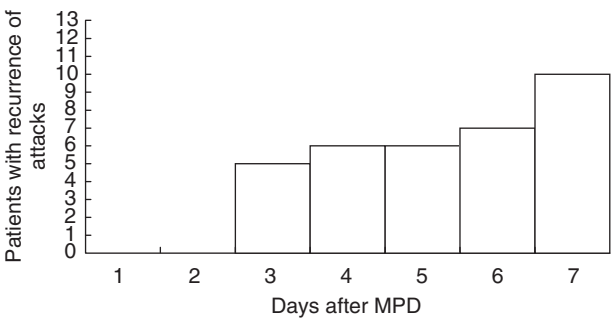

Figure 3 Recurrence of attacks after MPD ($n = 10$).

Prednisone and 6-alpha-methylprednisolone, at variance with betamethasone and dexamethasone, have similar anti-inflammatory potency, Na^+ retaining effects and duration of action (intermediate, i.e. 12–36 h of biological half-life), and act at equivalent doses (9). The different action may thus be partly explained by the peculiar regulation of gene expression exerted by these agents (10). There is no currently accepted standard for the administration of steroids in CH, although consensus recommendations and guidelines have been published (11).

According to current literature, and as far as effectiveness alone is concerned, prednisone can be considered as a first-line drug in episodic CH. This drug may be particularly helpful in those patients who, on the basis of previous experience, are expected to have a bout duration of no longer than 3–5 weeks at the time of initiation of the treatment. However, similar to what is commonly observable with indomethacin in chronic paroxysmal hemicrania (CPH) (12, 13), the disease process is only curbed, not extinguished, by steroids in CH.

To our knowledge, only one controlled trial (using prednisone) has so far been carried out (see Table 2 for the main previous studies). As in most other studies, the present one was carried out without a placebo control, but with each patient acting as his own control. In future studies comparisons with a control group could be carried out. Indeed, previous reviews on this subject suggest that there may be a placebo effect in CH (14, 15).

The aim of the present study was to elucidate whether a single, high-dose MPD treatment as monotherapy is able to maintain a stable clinical remission in episodic CH, preventing the patients from further pain episodes. In line with the findings obtained by Cianchetti et al. (7) in a single case, a relatively clear-cut response was obtained, which confirmed the short-term efficacy MPD, but also clearly demonstrate that there is a tendency to recurrence of attacks in the majority of patients.

Had MPD been effective in an absolute fashion, complete disappearance of attacks would have occurred: in fact, this was the case only in 23% of patients. The three patients with no further attacks may have experienced a spontaneous recovery: the previous active period in these patients had lasted 40, 55, and 14 days, respectively. In most of our patients, attack recurrence was reported after a short pain-free period (mean 3.8 days). On recurrence, the pattern of attack frequency was similar to that reported in the run-in period. The long-lasting benefit from a single bolus of MPD in interrupting the bout might be coincidental. In

Table 2 Studies on steroids in the prophylactic treatment of CH

Authors	Steroid	Dose and route of administration	Beneficial effect (%)†
Horton (1952) [16]	Cortisone	100 mg (= 20 mg prednisone)/orally	4/21 pts(20%)
Jammes (1975) ‡ [4]	Prednisone	30 mg/tapering off/orally	17/19 pts(90%)
Kudrow (1980) [4]	Prednisone	60 mg/orally	86% > 50% relief 75% > 75% relief
Couch & Ziegler (1978) [5]	Prednisone	80 mg/orally	58% complete relief
Prusinski et al. (1987) [6]	Dexamethasone or Depot-ACTH (adrenocorticotropin)	16 mg day 1; 8 mg day 2 i.v. 1 mg i.v. every 3rd day up to 12 mg	Pain free days within 2 days. Period interrupted
Anthony & Daher (1992) [2]	Dexamethasone	4 mg b.i.d 2 week, 4 mg/day 1 week/i.m.	Relief, but recurrence on tapering off.
Cianchetti et al. (1998) [7]	MPD	0.5–1 g/day/I.V.	One case; 4–5 days pain freedom
Mir et al. (2003) [3]	MPD + prednisone	MPD 250 mg i.v. Prednisone 90 mg orally	Relief in most patients

†Reduction of attack frequency or period interruption, ‡double blind controlled study. MPD, methylprednisolone.

clinical practice we are aware that in particular experimental circumstances (i.e. sleep recording in the hospital, clock-time rhythmicity of attacks, etc.) the regular pattern of attack may change or stop.

A recent report showed that 250 mg boluses of MPD on three consecutive days, followed by prednisone 90 mg/day orally, with gradual tapering in 4 weeks, induced a significant reduction of attack frequency in episodic CH for several weeks. However, these findings cannot be compared to our own results due to the different study design (type of drugs, doses, mode of administration). The drug was, moreover, introduced at different stages of the cluster period (mean 21.8 days after cluster onset) in the other study (3).

In agreement with previous studies, our data confirm that patients with episodic CH single, high-dose systemic steroid administration may invariably interrupt attack recurrence for a few days, but MPD is ineffective in maintaining complete clinical remission.

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Nitric oxide pathway and response to nitroglycerin in cluster headache patients: plasma nitrite and citrulline levels

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Nitric oxide (NO) may participate in the mechanisms underlying vascular headaches, such as migraine and cluster headache (CH), by triggering neurogenic inflammation and activation of fibres conveying nociceptive inputs to the trigeminal ganglion. Similarly to migraine, the administration of the NO donor glyceryltrinitrate (GTN) to CH patients is a known model of inducing spontaneous-like attacks. We carried out a GTN test (0.9 mg, sublingually) in 18 patients with episodic CH in active phase and 12 controls. The plasma levels of NO metabolite nitrites (NO_2^-), after conversion of nitrates to NO_2^-, were measured spectrophotometrically at baseline, at the maximum intensity of the induced response (or 45 min after GTN in controls), and 120 min after GTN administration. The basal plasma levels of L-citrulline were also assayed in patients and controls using high-performance liquid chromatography. Basal NO_2^- levels, similar in GTN-responsive patients and controls (48.3 ± 10.6 and 44.6 ± 9.5 μmol/l, respectively) were found to be increased significantly at pain peak in patients (76.1 ± 10.2 μmol/l) and after 45 min in controls (78.2 ± 9.6 μmol/l) ($P < 0.01$ vs. respective baseline values), but not after 120 min, without differences between groups. L-citrulline levels in basal conditions showed no differences between groups (patients 64.8 ± 11.7, controls 67.3 ± 10.8 μmol/l). These data do not support the presence of a basal hyperactivity of the L-arginine–NO pathway in CH patients. Increased NO production may be of importance in the mechanisms leading to CH attacks, but other factors are likely to render CH patients hyperresponsive to NO, and ultimately to cause the occurrence of pain and associated features. □*Citrulline, cluster headache, glyceryltrinitrate, nitric oxide, nitrites, trigeminovascular system*

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Introduction

While the clinical features of cluster headache (CH) are well defined, uncertainty still exists as to the precise pathophysiological mechanisms underlying the disorder. Autonomic dysfunction and cluster pain have been the aspects receiving most study, with considerable evidence suggesting that both phenomena may originate in the central nervous system (CNS). According to such view, CH patients may be characterized by derangement of the hypothalamic–limbic pathways subserving the autonomic, neuroendocrine and behavioural functions (1–3).

Various theories have been proposed to explain the generation of pain during CH attacks. CH is considered as a primary neurovascular headache, since it most probably involves activation of trigeminovascular pain structures projecting to the trigemino-cervical complex of neurones in the caudal brain stem and upper cervical spinal cord (4, 5). The sensory innervation of intracranial vessels, originating

in the trigeminal ganglion, includes several signalling neuropeptides, such as calcitonin gene-related peptide (CGRP), substance P, neurokinin A, pituitary adenylate cyclase activating peptide (PACAP) and vasoactive intestinal peptide (VIP); in particular, a clear association exists between head pain and the release of CGRP (6). However, in addition to classical neuropeptides, other factors appear to be involved in CH pain; among these, the unconventional gaseous transmitter nitric oxide (NO) appears to play an important role. Studies of headache induced by the administration of glyceryltrinitrate (GTN), an exogenous NO donor, and histamine, which induces NO release from vascular endothelium, have suggested that NO may be a key mediator in both migraine and CH (7). There is considerable evidence to indicate that NO release from blood vessels, perivascular nerve endings and brain tissue is an important molecular trigger mechanism in spontaneous headache pain (8). It has also been proposed that patients with vascular headaches may display excess NO production and/or increased response to the activation of NO-ergic pathways (9). The intimate nature of these processes remains unclear, but it is also known that the administration of GTN modulates neuronal activity in several brain areas, particularly the brain stem and hypothalamic nuclei, which are involved in vascular headaches (10). Thus, in addition to its effect at the endothelial level, NO may act centrally, thereby participating in the processes underlying the onset of pain as well as neurovegetative signs and symptoms in migraine and CH (11).

In migraine sufferers, the sublingual (12) or systemic (13) administration of GTN is able to precipitate headache attacks, whose features resemble those of the spontaneous episodes and fulfil the diagnostic criteria for migraine. This method still represents the most reliable and reproducible paradigm of induced headache of the vascular type in humans (14). Even though with different temporal modalities, spontaneous-like CH attacks can also be triggered in predisposed individuals by GTN administration, only in the active phase (15–17).

Nitrites (NO_2^-) represent stable inorganic end-products of NO metabolism (18). In this study, we have measured plasma NO_2^- levels in a group of CH patients, in basal conditions as well as during a spontaneous-like attack induced using the GTN model, with the aim of further elucidating the involvement of NO pathways in CH pathophysiology. Moreover, since L-citrulline, the stoichiometric metabolite resulting from the conversion of L-arginine to NO, is considered as a specific and reliable index of nitric oxide synthase (NOS) activity *in vivo* (18, 19), basal plasma L-citrulline levels have also been measured in patients and controls.

Methods

The selected study group consisted of 18 patients, 16 males and two females, presenting with headache at the Headache Centre of the Neurological Institute of the University of Pavia, and enrolled consecutively. All patients were suffering from CH in active phase, according to the International Headache Society criteria (20). All patients had appearances absolutely typical of CH, with a constant presence of autonomic accompanying signs and symptoms during their pain attacks (frequency of two to four attacks/day). Patients were aged between 35 and 63 years (mean ± SD 46.3 ± 8.6). The mean ± SD of symptom duration was of 8.5 ± 3.4 years (range 3–18 years), and that of the pain attacks was of 47.0 ± 11.5 min (range 25–70 min). The latter was calculated on the basis of at least five untreated attacks recorded by patients with a dedicated diary chart. The individual clinical features of the patients studied are reported in detail in Table 1.

Patients and controls had received a list of potential dietary sources of nitrates/nitrites, and had been instructed to avoid, for at least 48 h before blood sampling, the ingestion of sausages and other canned foods known to contain nitrites as preservatives. At the time of testing, patients were having regular headaches, and none of them had taken any prophylactic medication for at least 1 week prior to the study. After obtaining formal approval by the local Ethical Committee and informed consent by all subjects, a complete clinical history was collected.

As controls, we studied 12 healthy sex- and age-matched subjects (10 males, two females, mean ± SD age of 43.5 ± 8.4 years (range 34–61 years). In particular, none of them had ever suffered from headache or showed any family history of headache. Nine of the 18 patients and six of the control subjects were smokers.

After overnight fast, patients and controls underwent a standard headache-induction test, between 08.30 h and 09.30 h, carried out by administering GTN (trinitrine) 0.9 mg sublingually in headache-free conditions. This dose, currently used at our Department, has been found to induce typical pain attacks in 60–70% of CH patients in active phase (21), a percentage similar to that reported by Ekbom with 1 mg GTN (15). During each test, patients were resting in bed in a supine position, and their cardiopressor parameters (heart rate, arterial blood pressure)

Table 1 Clinical features of patients

Patient	Age (years)	Gender	Pain side	Cluster headache type	Symptom duration (years)	Attack duration (min)	Autonomic symptoms
1	35	M	R	Episodic	5	25	ci, nc, l
2	38	M	R	Episodic	6	35	ci, nc, r
3	63	F	L	Episodic	5	37	ci, nc, l, p, r
4	57	M	R	Episodic	3	70	ci, nc, l, r
5	54	M	L	Episodic	18	32	ci, nc, l
6	39	M	R	Episodic	10	39	ci, nc, l, p, r
7	41	M	L	Episodic	12	47	ci, l
8	38	M	L	Episodic	13	46	ci, nc, l, p, r
9	40	M	R	Episodic	8	51	ci
10	42	F	R	Episodic	8	49	ci, nc, l, r
11	42	M	L	Episodic	7	47	nc, p, l, r
12	47	M	L	Episodic	10	38	ci, nc, l
13	48	M	R	Episodic	9	48	ci, l, r
14	50	M	R	Episodic	8	64	ci, nc, l, r
15	55	M	R	Episodic	8	57	ci, l
16	39	M	L	Episodic	10	56	ci, nc, l, r
17	44	M	R	Episodic	7	48	ci, nc, r
18	62	M	L	Episodic	7	58	ci, l

Ci, Conjunctival injection; nc, nasal congestion; l, lacrimation; p, ptosis; r, rhinorrhoea. Attack duration refers to the usual duration prior to the study.

were continuously recorded using a vital sign monitor (Dynamap; Kriticon, Orlando, FL, USA). The time of onset of pain, the possible occurrence of general autonomic symptoms, and any changes in the degree of conjunctival injection, width of the palpebral fissure, pupillar diameter and nasal congestion (if present) were also recorded using a dedicated chart. Patients were asked to score the intensity of any provoked headache by means of a visuo-analogue scale (VAS) ranging from 0 to 10 (0 = no pain, 10 = unbearable pain). The duration of the attack, and the severity of headache and autonomic symptoms were assessed and reported in the chart. For ethical reasons, patients were free to ask for a rescue treatment (sumatriptan 6 mg s.c.) whenever required. At the end of each test, patients were also instructed to contact the Headache Centre the following day, to report on the status of their headache. During the test, blood samples (10 ml, in tubes containing sodium EDTA for nitrite and heparin for citrulline) were obtained from the cubital vein in basal conditions, at the peak of the pain response (in the case of patients) or after 45 min (in the case of control subjects), and 120 min after GTN administration.

For NO_2^- assay, the other end-products of NO breakdown, nitrates, were converted into NO_2^- by enzymatic reduction using nitrate reductase (Sigma, Milan, Italy) in the presence of nicotinamide adenine dinucleotide phosphate (NADPH). The Griess method was then used (22), without deproteinization, by addition to samples of equal amounts of sulphanilamide 1% and naphtylethylenamide 0.1% in phosphoric acid 0.25%, and incubation at room temperature for 10 min. Samples were then centrifuged and stored at –80 C, until final measurement of absorbance by spectrophotometric reading at 546 nm. The intra- and interassay coefficients of variation (CV) were 5% and 10%, respectively.

For L-citrulline measurement, samples were centrifuged at 4 C for 15 min at 2200 g and plasma stored at –80 C until assay. High-performance liquid chromatography (HPLC) equipment (Jasco Inc., Easton, MD, USA series LC-900), coupled with a fluorimetric detector, was used. Amino acids were separated using an inverse phase Waters Nova pak C18 column (4 µm particle size, 3.9 × 150 mm) at 25 C, at a 0.8-ml/min flow (linear gradient). After adding perchloric acid 0.4 N (1 : 1 v/v), samples were centrifuged for 15 min at 4 C. The supernatant was properly diluted with methanol (MeOH), and after addition of ophtaldialdehyde (OPA) the fluorescent derivative was analysed.

Statistical analysis of data was performed using the analysis of variance (ANOVA), where appropriate. Dunnett's correction for multiple comparisons was used to compare plasma NO_2^- levels during GTN

test with those obtained prior to GTN administration. Differences were considered significant if $P < 0.05$. Data are expressed as mean ± SD.

Results

Twelve of the 18 patients, all males, experienced a typical, spontaneous-like attack on the usual side, occurring in all cases within 45 min (mean ± SD of latency 32.5 ± 6.3 min, range 19–41 min). Pain peak was reached (and blood samples obtained) after 12.6 ± 2.9 min (range 8–18 min). Only four patients asked for the rescue treatment (sumatriptan 6 mg s.c.), which was administered after the second blood sampling with prompt relief. In the other patients, pain duration (range 30–60 min) and severity were reported as being similar to those of the usual attacks, as were type and intensity of autonomic signs and symptoms. The clinical features of the 12 GTN-responsive patients are reported in Table 2. As expected, none of the control subjects experienced pain or any autonomic signs or symptoms.

Baseline NO_2^- levels (Fig. 1) were similar in patients and controls, and were found to be significantly increased at pain peak in the patient group, and 45 min after GTN administration in the control group ($P < 0.01$ vs. respective basal levels). In both groups, 120 min after GTN administration, NO_2^- concentrations were no longer different from their baseline values.

Similar to NO_2^-, plasma L-citrulline levels in basal conditions were not different between groups (Fig. 2). In the six GTN-unresponsive CH patients, basal NO_2^- and L-citrulline levels, as well as NO_2^- levels during GTN test, were not statistically different from those of GTN-responsive ones (data not shown).

No significant correlations were found between NO_2^- or L-citrulline levels and the clinical features of patients, such as age and disease duration.

Discussion

Our findings further confirm the previously reported (15–17, 21) ability of GTN to trigger a spontaneous-like attack in a high percentage of CH patients in active period of disease. The reasons for the observed differences in the clinical response to GTN (which can be variably delayed or even absent) are still unclear, and it has been supposed that the type of response may be related to the individual characteristics of the patients investigated (15, 17).

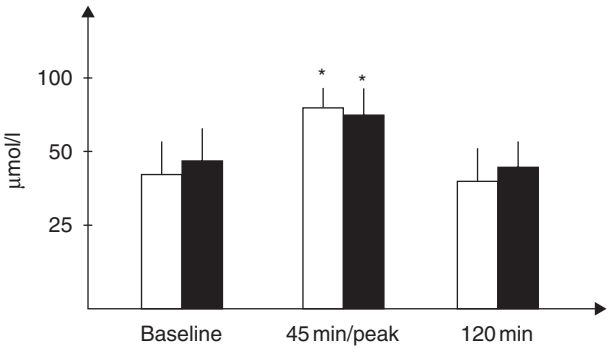

Figure 1 Mean ± SD of plasma levels of NO_2^- (µmol/l) in basal conditions and during glyceryltrinitrate test in 12 cluster headache patients ( ) and 12 control subjects (□). *$P < 0.01$ vs. respective baseline values. Patients vs. control subjects: NS.

Table 2 Clinical features of the 12 glyceryltrinitrate-responsive patients during induction test

Patient	Age (years)	Sex	Latency of induced pain (min)	Side of induced pain	Autonomic symptoms
1	35	M	19	R	ci, nc, l
4	57	M	41	R	ci, nc, l
5	54	M	29	L	ci, nc, l
6	39	M	36	R	ci, nc, l, r
7	41	M	38	L	ci, l
8	38	M	32	L	ci, nc, l, p, r
11	42	M	30	L	nc, l, r
12	47	M	29	L	ci, nc, l
14	50	M	40	R	ci, nc, l, r
15	55	M	30	R	ci, l
16	39	M	38	L	ci, nc, l
18	62	M	28	L	ci, l

See Table 1 for abbreviations.

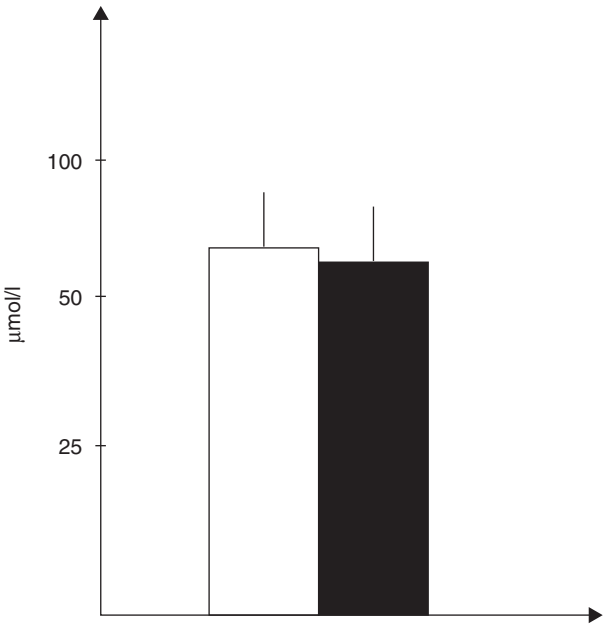

Figure 2 Mean ± SD of basal (interictal) plasma levels of L-citrulline (µmol/l) in 12 cluster headache patients ( ) and 12 control subjects (□). Patients vs. control subjects: NS.

However, in both GTN-responsive and unresponsive CH patients, we found basal NO_2^- concentrations similar to those of control subjects. Robust evidence obtained from different experimental models has suggested that L-arginine–NO pathways may be hyperactive in vascular headaches, both during and outside of attacks (23–27), although there are recent inconsistent observations (28). D'Amico et al. found significantly higher NO_2^- concentrations in a wide population of CH patients (in either remission or cluster period) compared with controls (27). However, there was no measurement of NO_2^- concentrations during spontaneous or induced attacks, the authors suggesting that a basal dysfunction in the L-arginine–NO pathway may be involved in the peripheral mechanisms predisposing subjects with neurovascular headaches to individual attacks. By contrast, in another study Martelletti et al. were unable to find increased NO_2^- levels in serum and peripheral blood mononuclear cell supernatants from CH patients in the interictal period (26), an observation apparently consistent with our findings. It is difficult to account for these discrepancies, but it is known that even in spite of dietary restrictions or other precautions, NO_2^- concentrations can be significantly affected by several variables, such as alcohol, cigarette smoking, atmospheric pollution and exercise (29). L-citrulline is a metabolite which represents a further specific index of activation of the biological pathway leading to NO production (18, 19). In any experimental paradigm, changes in L-citrulline values, when consistent with those of NO_2^-, would strengthen the reliability of the findings with respect to NO metabolism. However, to our knowledge there is no previous report in literature on the levels of circulating L-citrulline in patients with neurovascular headaches. In the present study, as already seen for NO_2^-, we were unable to find differences in plasma L-citrulline concentrations between controls and CH patients in the interictal period. Therefore, the concomitant observation of 'normal' basal levels of the two principal end-products of NO generation, NO_2^- and L-citrulline, would suggest that at least in basal, headache-free conditions there is no increased activation of NO pathways in CH patients.

With particular regard to NO involvement in the attack, NO_2^- concentrations in our patients were significantly increased at the time of maximum severity of pain following GTN administration, whereas they were no longer different from their basal values after 2 h. This observation is in line with a previous report in CH patients during spontaneous and NO donor-induced pain attacks (26). In our study, however, a similar trend was also shown by the control group, in which NO_2^- concentrations were increased (in the absence of any pain or other symptoms) 45 min after GTN administration, i.e. when the totality of responsive CH patients were already experiencing their GTN-induced attack. It would therefore appear that NO_2^- concentrations, which reflect the release and breakdown of native NO plus the amount of NO directly liberated by GTN, increase in a similar manner in normal subjects and CH patients, but are associated with genuine pain attacks only in the majority of the latter group. Indeed, a similar profile of NO_2^- concentrations was shown by the six CH patients who did not experience a typical attack after GTN.

There are some limitations to be considered in this study. From a single sample obtained at pain peak it is impossible to infer whether NO_2^- peak precedes or follows the onset of headache. In this respect, more frequent sampling would be helpful in further studies. In addition, peripheral blood may not be the best specimen in which to measure changes in NO production. The systemic compartment may be too large and small local changes may not be detectable, unless the investigation is focused, for example, on jugular blood. Furthermore, within a setting of GTN-induced attacks it is difficult to draw reliable conclusions on NO involvement in pain generation, as the provoking agent could mask spontaneous changes. To this purpose, NO changes should be studied also during genuine CH attacks. However, even with

these limitations, our data suggest that other factors may sensitize predisposed individuals to the effects of NO (either exogenously loaded using donors, or generated during a spontaneous attack), ultimately causing pain. As in migraine, neurogenic inflammation and activation of the trigeminovascular system may be critical in CH pathophysiology (5, 6, 16), despite some conflicting evidence (30). Neurogenic inflammation is characterized by the release of several vasoactive agents from trigeminal perivascular nerve endings, leading to vasodilation, plasma protein extravasation, and sensitization of sensory afferents conveying nociceptive inputs to the brain stem (31). Increasing evidence indicates that NO may play a considerable role in these events, as it stimulates the release of the potent vasodilating agent CGRP from perivascular trigeminal fibres in cats (32, 33). Consistently, in humans CGRP levels are increased in the external jugular vein during NO donor-induced CH attacks (5, 16), as well as during genuine migraine attacks (34). NO is also present in nerve fibres surrounding cerebral blood vessels (35), induces protein extravasation from the vessels of the dura mater (36), and facilitates nociceptive transmission from the periphery to the CNS (37). Since the simple dilation of cerebral and extracerebral blood vessels does not appear to be a fundamental mechanism in GTN-induced pain in CH (38), GTN may trigger CH pain by stimulating trigeminal nociceptive fibres to release CGRP (16). Dural meningeal vessel dilation may later occur (32), according to a process probably requiring considerable time, if one looks at the usual latency of GTN effect (19–41 min in this study). In line with this view, inhibition of NOS significantly attenuates the activation of the trigemino-cervical complex of the cat (8) and antagonizes neurogenic and CGRP-induced dural vessel dilation (39). NO may also act within the brain stem nuclei of CNS, thereby contributing to the process of central sensitization and the development of pain and autonomic signs and symptoms. GTN-released NO can indeed activate several relevant areas in the CNS, such as the trigeminal nucleus caudalis (10, 40), and modulate the function of neurotransmitter pathways (41, 42). Interestingly, it has been suggested that an up-regulation of the expression of soluble guanylyl cyclase (the NO target enzyme) as well as cytokines in the dura mater may account for the subacute or delayed onset of GTN-induced symptoms (43, 44). Such phenomena may occur in CH, and may be one possible explanation for our finding that CH patients experienced spontaneous-like attacks in spite of a NO availability apparently similar to that of control subjects.

In conclusion, we have found in CH patients in the interictal phase that the plasma concentrations of the two main NO metabolites, NO_2^- and L-citrulline, do not differ from those of headache-free subjects. This does not support the presence of a basal hyperactivity of the L-arginine–NO pathway in CH patients. NO_2^- values are significantly elevated during the GTN-induced attacks in the patients, but in a fashion similar to those of control subjects at the corresponding time. Therefore, other factors, presently unclear, may render CH patients hyperresponsive to NO, and ultimately cause the occurrence of pain and associated features. Further studies are awaited to better understand NO involvement in CH and other vascular headaches.

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Parenteral indomethacin (the INDOTEST) in cluster headache

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The interval between indomethacin administration and clinical response may be extremely relevant in the assessment of chronic paroxysmal hemicrania (CPH) and other unilateral headache disorders like cluster headache (CH), with which CPH can be confounded. Indomethacin is inactive in CH; however, in some anecdotal reports in recent years, doubt has been cast on the ineffectiveness of indomethacin in CH. In this study, we have re-assessed the effect of indomethacin treatment in a group of 18 patients with episodic CH (three females and 15 males). From the day 8 of the active period, indomethacin 100 mg i.m. was administered every 12 h, for 2 consecutive days, in an open fashion. The mean daily attack frequency before the test (1.6 ± 0.6) was not statistically different from that on day 1 (2.1 ± 0.9) and day 2 (1.9 ± 0.8) after indomethacin administration. The mean interval between indomethacin injection and the following attack (day 1 and day 2) was 4.6 + 1.1 h. We did not observe any refractory period in any patient after indomethacin. Since the 'expected' attack occurred when there theoretically could have been a protective effect after indomethacin administration, it can be reasonably assumed that there is no such protective effect. The use of a test dose of 100 mg i.m. indomethacin (INDOTEST) appears to provide a clear-cut answer in this situation. It may be a useful tool for a proper clinical assessment of unilateral headache with relatively short-lasting attacks when problems of classification arise. A correct diagnosis of CPH or CH is important, since a CPH diagnosis may imply a lifelong treatment with a potentially noxious drug. □*Cluster headache, chronic paroxysmal hemicrania, indomethacin, diagnostic criteria, symptomatic treatment*

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Introduction

Chronic paroxysmal hemicrania (CPH) is a strictly unilateral headache disorder, characterized by an absolute responsiveness to indomethacin (1, 2). Since the indomethacin response is a fundamental element in establishing the differential diagnosis vs. cluster headache (CH), it is extremely important that this pharmacological test be conducted in an optimal way. In recent literature, there are several reports in which a dubious diagnosis of CPH has been made on the basis of hazily or even erroneously executed indomethacin tests.

It was demonstrated many years ago that indomethacin is ineffective in CH: 10 CH patients suffering from either the episodic or chronic variety of CH were treated with oral indomethacin, in an open fashion; the treatment was of no benefit (1). Similarly, Bogucki (3) treated a CH patient with the chronic form and an unusually high frequency of attack with oral indomethacin and with no clinical response.

Moreover, in two cases with coexisting CH and CPH (4), oral indomethacin provided an absolute effect as regards the CPH part of the picture, but not the CH part, while verapamil was effective only against the latter.

However, some slightly disturbing reports have also appeared: in one report with an alleged coexistence of CH and CPH, the authors claimed that the results were less clear-cut, with a putative effect of indomethacin on the alleged CH part of the complex picture (5). It goes without saying that nosographic and interpretation problems have been immense in a case like this. A case of this nature is not particularly suitable for drawing sweeping conclusions.

The indomethacin-responsive episodic CH case reported by Geaney (6) was, however, probably not a true CH, but a case of the remitting form of CPH, masquerading as CH. Likewise, the clinical data regarding the patient described by Klimek (7) appear to be so indistinct that any firm conclusion can hardly be drawn from it. These anecdotal case reports are obscure and bewildering. The fluctuating course of CH makes drug effect difficult to assess in many cases. These cases should accordingly be reconsidered in this light. They may, nevertheless, to some extent have cast doubt on the original, clear-cut message: that of non-effectiveness of indomethacin in CH.

The aim of the present study was therefore to search for further confirmatory evidence for the ineffectiveness of indomethacin in CH. In doing so, we intended to optimize the conditions for indomethacin bioavailability by administering the drug parenterally.

Patients and methods

Patients

The present series consisted of 18 episodic CH patients, all in the active period of disease (three females and 15 males, aged 44 ± 16 years, mean ± SD). The diagnosis was established according to the International Headache Society (IHS) criteria (8). Non-hospitalized patients followed in the out-patient clinic were asked to fill in a headache diary from the first day of the cluster period for 7 days onwards; after this run-in period, the indomethacin test ('INDOTEST') (9) was carried out. Subcutaneous sumatriptan injection was allowed for treatment of attacks in the run-in period and during breakthrough attacks during the test. The study design is shown in Fig. 1.

Methods

Since in CPH patients the time span between indomethacin administration and attack recurrence was previously found to be longer after 100 mg than after 50 mg indomethacin (i.e. 10.4 ± 2.5 h vs. 8.2 ± 4.8 h, respectively) (9), the former dose was chosen. The test was carried out by invariably administering indomethacin from day 8: 100 mg intramuscularly at 8.00 a.m. and 8.00 p.m. for 2 consecutive days. The effect of indomethacin on any ongoing actual CH attack was not the aim of the present study. Attacks did not occur during or right after injection. The 'protective' effect of 100 mg indomethacin i.m. is known to start between 22 and 73 min after drug administration (9). Sumatriptan 6 mg s.c. was allowed in the event of attacks materializing during the test, in order to ameliorate the suffering. This would naturally prevent attacks for 3–4 h.

In order to assess the response during the test, the following parameters were evaluated: (i) the mean daily attack frequency over 7 consecutive days prior to the first injection and during the 2 days of the test; (ii) the mean duration of attacks prior to indomethacin injection and during the 2 days of the test; (iii) the mean interval between indomethacin injection and the first subsequent attack.

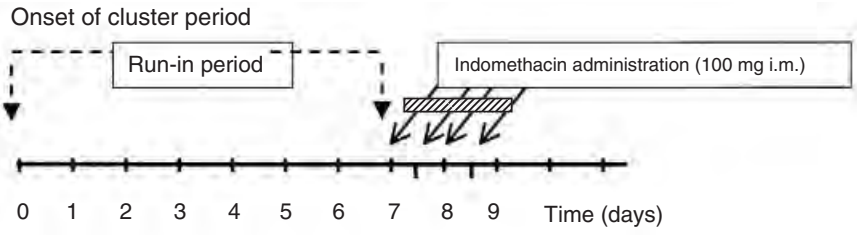

Figure 1 Cluster headache and INDOTEST: schematic illustration of the temporal relationship between the onset of the cluster period and indomethacin administration. Hatched bar denotes the expected refractory period under indomethacin regimen (in case of clinical efficacy of indomethacin).

The beginning of the cluster period is likely to be the most pertinent one for the evaluation of drug efficacy. The chances of a spontaneous stop in the flow of attacks increase with the advance of the bout. By adhering to the model described, a fast and reliable answer to a possible protective effect of parenteral indomethacin during the 48-h treatment period could be obtained.

Statistical analysis

The statistical evaluation of the attack frequency before and after indomethacin administration was carried out using the Friedman's test, while the Wilcoxon test for paired data was applied when comparing attack duration before and during the test period (day 1–day 2).

Results

In our patient series, the previous mean cluster period duration had been 35.7 + 12.4 days, while the mean duration of the penultimate period had been 31.2 ± 10.9 days. As shown in Table 1, there was no significant difference between the mean daily attack frequency during the 7 days preceding the test (1.6 ± 0.6) and that of day 1 and day 2 of the indomethacin test (2.1 ± 0.9 and 1.9 ± 0.8, respectively; $P = 0.073$ and $P = 0.074$, Wilcoxon test). Attack duration (with sumatriptan s.c. being given immediately upon attack onset) was similar before and during the test (11.5 ± 2.2 min and 10.9 ± 2.5 min, respectively) (Table 1). Not too much emphasis can be put on these figures, due to the interference of sumatriptan. From our data, the influence of sumatriptan injection on the forthcoming attacks may partly affect the test: the peak plasma concentration after injection being 14 min (10) and the effect duration 3–4 h. Emphasis was put on the occurrence of attacks within the 'window' of indomethacin protection. The mean interval between indomethacin administration and the first subsequent attack was 4.6 + 1.1 h, with attacks at times appearing even after 3 h. These data definitively confirm that within the expected refractory period of 7.5–13 h following 100 mg parenteral indomethacin, there is no protection from the drug.

Discussion

In our opinion, controlled experiments in drug studies should actually not be necessary in CPH and CH with daily recurring short-lasting attacks, unlike in other headache forms, such as migraine. The main reason for this is that, to the best of our knowledge, a placebo effect is apparently mild in CH (11, 12), while it has never been properly demonstrated in CPH (1, 12).

Our study was carried out according to an uncontrolled design, although in CH patients the use of placebo may be as important as in other cases (11, 12).

The purpose of the present study was to reconfirm the lack of protective effect of an indomethacin regimen in CH patients, employing the recently developed parenteral indomethacin test (INDOTEST). A clear-cut answer was obtained, and the non-efficacy findings of the original study were confirmed (1).

Table 1 Clinical features of cluster headache patients before and during INDOTEST

	Before indomethacin test	During indomethacin test	
		(Day 1)	(Day 2)
Attack frequency/24 h	1.6 ± 0.6	2.1 ± 0.9*	1.9 ± 0.8**
(range)	(1–3)	(0–4)	(0–3)
Attack duration in connection with sumatriptan injection (min)	11.5 ± 2.2	10.9 ± 2.5***	
(range)	(8–15)	(7–15)	
Interval between injection and first subsequent attack (h)	–	4.6 ± 1.1****	
(range)		(3–7)	

*$P = 0.073$ (Wilcoxon test, prior to indomethacin vs. day 1).

**$P = 0.074$ (Wilcoxon test, prior to indomethacin vs. day 2).

***$P = 0.227$ (Wilcoxon test, prior to indomethacin vs. during test).

****$p = 0.000$ vs. the range of presumed protective period under indomethacin regimen (i.e. 10.4 ± 2.5 h) (9).

For indomethacin to have been effective a complete disappearance of attacks would have been essential during the test. Similarly, it would have been extremely relevant that any attacks recurring during the test would have displayed a pain pattern close to that of the pretest phases.

The less suitable period for investigating the effect of pharmacological treatments in CH is the medium–late phase of a cluster period, when the chances of a spontaneous recovery are high. Accordingly, we chose in our study the onset of a cluster period, with a well-established headache pattern.

The rationale for carrying out the INDOTEST in CH patients is debatable. In principle, it may not be advisable to perform this test when the patient has less than one attack/24 h. In patients with three to four or more attacks per 24 h, the differential diagnosis vs. CPH may be more involved. In such a case, a fast and reliable differential diagnostic answer can be obtained by the INDOTEST. In this situation, repeated parenteral administration of 100 mg indomethacin will allow for a protective period of 10.4 ± 2.5 h in case of CPH. In countries where parenteral indomethacin is not available, one should use the oral build-up dose strategy for the differential diagnosis in unclear cases (13).

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3D kinematic analysis and clinical evaluation of neck movements in patients with whiplash injury

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In recent decades whiplash injuries, being a major reason for compensation claims, have become increasingly important in forensic medicine. In view of this, a reliable diagnostic method of assessing cervical range of motion (ROM) is needed. The aim of the present study was to evaluate neck function with a 3D kinematic method compared with clinical evaluation in whiplash injury. Seventy consecutive patients (M/F = 18/52) with a history of whiplash injury (WH) and 46 healthy volunteers (M/F = 24/22), mean age, respectively 33 ± 9 and 28 ± 6 years (mean ± SD) entered the study. Patients suffered from neck pain and/or unilateral headache. A computerized kinematic analysis of the ROM (Elite system) using passive markers and two infrared TV cameras was used. Clinical evaluation of active ROM was also performed both in patients and in 61 controls (M/F = 23/38; mean age 47 ± 18 years). Thirty out of 70 patients were tested at the time of their first consultation (T0) and 6 months later (T6), and 12 were also followed up after a year (T12). All neck movements, except extension, were significantly reduced in WH subjects compared with controls, in particular lateral bending. Comparing ROM at T0, T6 and T12, no significant differences were found. A global index of motion (GIM), obtained by calculating the sum of ROM in absolute value for all the movements acquired, was significantly reduced in WH compared with control subjects. The interobserver reliability of the clinical evaluation was globally acceptable. On the basis of the clinical evaluation, a significantly reduced ROM was found in all movements in WH subjects compared with an age-matched population. Computing the number of impaired cervical movements (ICMs), a significantly higher number was observed in WH patients than in controls, showing a decreasing trend at T6 and T12, with a significant improvement at T6 vs. T0. The computerized study of neck ROM may constitute a useful tool in the evaluation of WH at baseline and follow-up. □ *Kinematic analysis, whiplash, neck movement, cervicogenic headache*

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Introduction

In recent decades, many attempts have been made to obtain an objective method of assessing cervical spine mobility (1–9). Indeed, because of the complexity of the cervical joint apparatus, clinical evaluation alone may not be adequate in all situations. Furthermore, cervical spine mobility is thought to be influenced by ageing, biomechanical factors and degenerative processes. Thus, neck movement analysis is of clear clinical importance and requires a technique that is neither invasive nor complex to perform, and that provides reliable parameters. While for routine evaluation a rough clinical assessment based upon pure subjective evaluation may be sufficient, in case of cervical anaesthetics procedure or evaluation of certain treatment, a much higher degree of resolution should be used.

The function of the cervical spine has been kinematically examined in the past, using sequences of lateral X-rays, usually of the flexion-extension range of motion

(ROM) (2–4, 8), and cineradiography (5). However, given the considerable difficulty involved in obtaining diagnostically and clinically useful information from the vast amount of data produced by the computerized reconstruction and elaboration of neck movements (2–4, 8), these techniques were progressively discarded.

Thus, several instruments such as goniometers (1, 7, 9–13) and inclinometers/cybex (14–16) have been developed for the non-invasive evaluation of cervical spine movement. Although these devices are easy to use, not expensive and some of them have also shown reliability (9–13), they have proven to be cumbersome for patients (11), and to require the intervention of skilled examiners. Inclinometers, in particular, although easy to use, quick and inexpensive, have shown a relatively low level of intraobserver reliability (1, 15).

Recently, different studies (17–20) have been conducted to obtain a 3D kinematic analysis model of the anatomical head–neck structure by means of opto-electronic scanners. Such instruments were developed to quantify ROM and analyse qualitatively other parameters like the pattern of curvature, centre of rotation, etc. Furthermore, 3D kinematic evaluation of cervical ROM has been shown to be useful in assessing the coupled joint motion (17) that occurs at different levels in the cervical spine, in order to identify 'abnormal' mobility and thereby to improve the accuracy of motion analysis.

The method used in the present study allows the measurement of the active ROM during the execution of head flexion-extension, lateral bending and axial rotation movements by means of an *ad hoc* 3D anatomical model (21).

Since the pathogenic substrate of neck sprain is still far from being known, it is a demanding task to unravel putative and subtle abnormalities using more sophisticated 3D studies.

The aim of the present work was to evaluate the usefulness of a 3D kinematic method, compared with the clinical evaluation, in the study of neck function in whiplash injury, in order to quantify any impairment of cervical spine mobility (21) and the outcome of the disease.

Patients and methods

Patients

Seventy consecutive patients (M/F = 18/52), referred to the 'C. Mondino Foundation', with a history of whiplash injury and 46 healthy volunteers (M/F = 24/22), mean age, respectively 33 ± 9 and 28 ± 6 years, entered the study. Patients included were required to have sustained a whiplash injury more than 1 month earlier. The illness duration was ≤ 1 year in 42 patients (5 ± 3 months; ≤ 6 months in 26 of these) and > 1 year in 28 (49 ± 30 months). In accordance with the Quebec Task Force (QTF) Classification of Whiplash Associated Disorders (WADs) (1995) (22), 56 patients were diagnosed as grade 2 and 14 as grade 3. All of them suffered from neck pain and/or unilateral headache (if bilateral, the pain was predominant on the same side).

Thirty-eight subjects had been involved in a rear-end collision and 6 in a frontal collision; in 14 patients neck sprain resulted from a lateral impact, while in 12 a mixed mechanism was described.

All patients were tested with the Elite at the time of their first consultation (T0). Thirty of them were re-examined 6 months later (T6) and 12 of these 30 patients were also followed-up at 12 months (T12).

A pure clinical evaluation of active ROM was also performed both in the 70 whiplash injury (WH) patients (M/F = 18/52) and in 61 historical controls (M/F = 23/38; mean age 47 ± 17.9 years). An age-matched group of 45 subjects (M/F = 9/36; mean age 37.5 ± 11.6 years), selected from the historical control group, was compared with the WH patients. The series of controls denied any head/neck trauma and/or any history of headache (migraine, episodic tension-type headache (TTH) > 1 day/month) or neck pain.

Methods

Patients were evaluated using a structured interview and screened by means of a questionnaire applying the diagnostic criteria for cervicogenic headache (CEH) (23, 24), migraine without aura (M) (IHS) and headache associated with neck disorders (HN) (IHS Classification Committee, 1988) (25). On the basis of IHS diagnostic criteria, after a 3-month well-documented retrospective history recording, patients with TTH were excluded. At the time of the first consultation the litigation was still open while at 6-months follow-up any claims were resolved.

Neck movement assessment

In order to assess cervical spine movements, computerized kinematic analysis (Elite system) was performed by means of passive markers and two infrared TV cameras working at a sampling rate of 50 Hz. The Elite system (B|T|S, Milan, Italy), a TV image processing system, supplies the 3D co-ordinates of all visible markers, evaluating cervical spine ROM with respect to the trunk (degrees) (Fig. 1). The kinematic model developed required the reconstruction of six anatomical points, three of them describing the head and the other three describing the trunk. The selected points are shown in

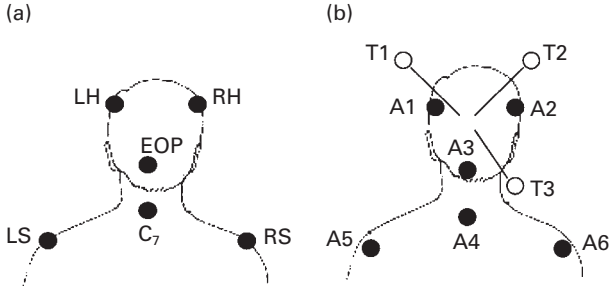

Figure 1 (a) Basic marker set-up on head and trunk while the subject is still. The markers are as follows: (LH) left and (RH) right sides of the head (located 4 cm either side of head vertex); EOP, external occipital protuberance; C7, seventh cervical vertebra; (LS) left and (RS) right shoulders on the acromion protuberance. (b) Technical markers (T1–T3) and anatomical markers (A1...A6) during the anatomical calibration procedure.

Fig. 1. The reliability of this system has been demonstrated in a previous study (21).

The subject was comfortably seated and looking straight ahead before performing each recording session, with shoulders and thorax kept in a fixed position to guarantee the selective measurement of the cervical spine movement.

To avoid disturbances on acquired data because of hair movement, the subjects were wearing special elastic cotton caps fixing and hiding their hair.

The subjects were asked to perform, in sequence, the following active movements: head flexion-extension, lateral bending and axial rotation. Each movement was repeated five times with no pauses in between. The sequences had to be performed at natural cadence, aiming to obtain the maximum ROM. The mean of three movements (excluding the highest and lowest ones) was taken as the real ROM value. Further details on the apparatus and the mathematical reconstruction of marker co-ordinates have been provided by Bulgheroni et al. (21). Zero degree was taken as the neutral position and the ROM was calculated as an absolute value (21).

In the present study, we also calculated a global index of motion (GIM), as the sum (in degrees) of the ROM in absolute value for all the movements acquired. Moreover, the percent variation, compared with baseline (T0), of each movement at T6 and T12, respectively, was also calculated.

Two experienced examiners performed clinical evaluation, assessing right and left flexion, right and left extension-rotation, right and left flexion-rotation, right and left lateral flexion, right and left rotation. ROM was clinically assessed as follows: 0 = 100% dysfunction, 1 = 75% dysfunction, 2 = 50% dysfunction, 3 = 25% dysfunction, 4 = no dysfunction, where dysfunction stays for reduced functionality of neck movement. Furthermore, the number of impaired cervical movements (ICMs) was also computed as the sum of movements with a score ranging from 0 to 3, i.e. with a decreased ROM.

Statistical analysis

The data were analysed using the statistical program SPSS for Windows (version 6.3).

One-way ANOVA was applied to compare the 3D kinematic analysis of cervical spine movements in patients with that in controls.

The intraclass correlation coefficient (ICC) was, as described by Fleiss (26), calculated for each movement assessed by clinical evaluation. The ICC is the fraction of variance calculated by the variation between subjects. Thus, if the variance between tests (or examiners) is small compared with the variance between subjects, then the ICC is close to 1. According to Fleiss (26), ICC values >0.75 generally mean 'excellent'. Paired Student's *t*-test was applied to assess whether the mean differences between examiners were significantly different from zero. A two-sided *P*-value of 0.05 was regarded as significant.

The non-parametric Mann–Whitney *u*-test was performed to assess possible differences in the clinical evaluation of cervical ROM between WH patients and healthy subjects ($n=46$), while the non-parametric Kruskal–Wallis test was applied between groups of patients with different illness durations.

ANOVA for repeated measures (with Bonferroni's test) was applied to compare 3D kinematic, as well as ICM, data at T0 vs. those at T6 and at T12. The non-parametric Friedman's test was used to compare clinical data at different times of consultation.

Results

On the basis of the relevant criteria, the following diagnoses were obtained: CEH (Sjaastad et al. 1990) ($n=24$) 34.3%; M (IHS) ($n=8$) 11.4%; HN (IHS) ($n=10$) 14.3%; CEH + M ($n=8$) 11.4%; CEH + HN ($n=6$) 8.6%; non-classifiable ($n=14$) 20%. The relation between headache and whiplash has not been the object of the present study.

Kinematic analysis

All neck movements, with the exception of extension, were significantly reduced in WH patients with whiplash injury compared with controls ($n=46$) ($P<0.05$), in particular right and left bending ($P<0.005$) and left rotation ($P<0.005$) (Fig. 2). Grouping patients according to the QTF scoring system, no significant differences in

ROM were found when CEH patients were compared with those with no CEH.

WH patients with a recent whiplash (≤1 year) showed a somewhat reduced ROM (in particular left rotation) when compared with those with an illness duration >1 year. Furthermore, subjects with a neck sprain within the previous 6 months showed significantly reduced neck extension in comparison with patients with a longer illness duration (>6 months) ($P<0.05$) (Fig. 3).

The GIM, calculated as the sum of the ROM of all the movements acquired, was significantly reduced ($P<0.005$, ANOVA one-way) in WH patients ($252^\circ \pm 66^\circ$) compared with controls ($310^\circ \pm 59^\circ$) (Table 1). Furthermore, patients with a recent whiplash injury (≤6 months) ($233^\circ \pm 73^\circ$) showed a slightly, non-significantly reduced ROM when compared with those with a longer disease duration ($262^\circ \pm 60^\circ$); the same result was produced by comparing patients who had sustained a neck sprain within the previous year ($237^\circ \pm 68^\circ$) with those with a longer whiplash history ($273^\circ \pm 58^\circ$).

No significant correlation was found between ROM and WAD score (QTF Classification) (22), and, respectively, headache diagnosis, type of collision and pain side.

Comparing ROM at 12-month follow-up with T0 and T6, no significant differences emerged, even though for some variable cervical spine mobility showed a trend towards improvement. When comparing T6 vs T0 only left rotation was significantly improved (Table 2).

The mean percent variation of cervical ROM for each movement was also calculated (Table 3); at T6 a relatively small increase (<30%) was noticed but, due to the large standard deviation, no relevance was attached to the finding.

When T12 was compared with T0 a large percent increase (>50%) was recorded in right and left lateral bending, with a significant improvement emerging in right lateral bending when comparing T0 with T6 and with T12 data ($P<0.05$, ANOVA for repeated

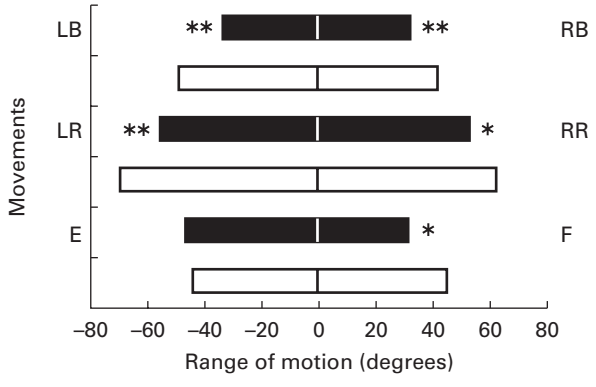

Figure 2 Cervical range of motion (ROM) assessed by 3D kinematic analysis in whiplash patients (WH) and in controls (Co). E, Extension; F, flexion; LR, left rotation; RR, right rotation; LB, left bending; RB, right bending. One-way ANOVA, WH vs. Co. □, Co ($n=46$); ■, WH ($n=70$). *$P<0.05$; **$P<0.005$.

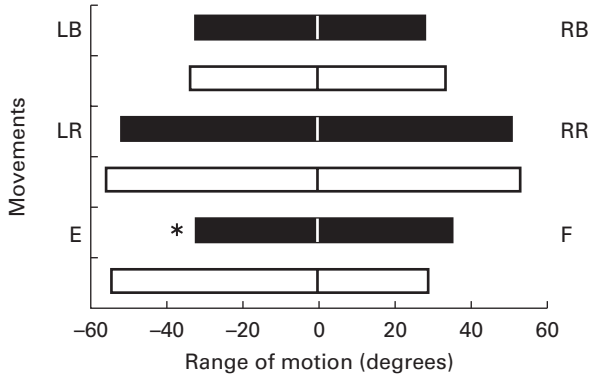

Figure 3 Cervical range of motion (ROM) assessed by 3D kinematic analysis in patients with a recent whiplash (WH≤6 months) and in those with a longer illness duration (WH>6 months). E, Extension; F, flexion; LR, left rotation; RR, right rotation; LB, left bending; RB, right bending. ■, WH≤6 months ($n=26$); □, WH>6 months ($n=44$). *$P<0.05$, Kruskal–Wallis.

Table 1 Global index of motion (GIM) in whiplash patients at T0, grouped as whiplash (WH) ≤6 months and >6 months, at T6, at T12 and controls (Co)

	GIM mean ± SD (°)
WH (T0) ($n=70$)	252 ± 66*
WH≤6 months (T0) ($n=26$)	233 ± 73
WH>6 months (T0) ($n=44$)	262 ± 60
WH (T0) ($n=30$)	211 + 51
WH (T6) ($n=30$)	228 ± 46
WH (T12) ($n=12$)	218 ± 58
Co ($n=46$)	310 ± 59

*$P<0.005$; ANOVA one-way vs. Co.

Table 2 Cervical range of motion (ROM) assessed by 3D kinematic analysis at the first consultation (T0) and at the 6-month follow-up (T6) in whiplash patients ($n=30$)

Movement	T0	T6
Flexion	25.59 ± 19.69	17.89 ± 24.72
Extension	31.58 ± 13.46	29.16 ± 9.48
Right lateral bending	29.64 ± 11.32	32.15 ± 5.67
Left lateral bending	32.27 ± 10.37	34.78 ± 9.00
Right rotation	48.18 ± 16.47	46.07 ± 14.57
Left rotation	50.72 ± 16.85	57.54 ± 12.29*

Values are expressed in degrees.
*$P<0.05$; Student's paired *t*-test.

Table 3 Percent variation of range of motion (ROM) evaluated with 3D kinematic analysis in whiplash patients

	Movements	Cervical ROM, % variation (mean ± SD)
T6 vs. T0 ($n=30$) ((T6–T0)/T0)	Extension	22.8 ± 117.5
	Flexion	44.1 ± 204.5
	Right bending	25.4 ± 53.6
	Left bending	21.0 ± 45.9
	Right rotation	8.7 ± 63.9
	Left rotation	19.8 ± 30.7
T12 vs. T0 ($n=12$) ((T12–T0)/T0)	Extension	−20.6 ± 16.2
	Flexion	6.7 ± 49.5
	Right bending	56.2 ± 63.9
	Left bending	67.0 ± 98.2
	Right rotation	31.2 ± 72.4
	Left rotation	−12.9 ± 76.0
T12 vs. T6 ($n=12$) ((T12–T6)/T6)	Extension	5.5 ± 51.8
	Flexion	9.6 ± 20.4
	Right bending	−0.3 ± 22.9
	Left bending	12.8 ± 33.8
	Right rotation	−0.7 ± 18.0
	Left rotation	−35.1 ± 68.4

measures) (Table 3). No major differences were found when comparing ROM at T12 and at T6.

No significant difference in GIM emerged when data from the time of the first consultation were compared with those at the T6 and at the T12 follow-up.

Clinical evaluation

The interobserver reliability of the clinical evaluation, computed according to Fleiss (26), was good for all movements (0.68–0.86) with the exception of left lateral flexion (ICC = 0.47) (Table 4).

At clinical evaluation, WH patients showed a decreased ROM compared with age-matched controls, as shown in Table 5. Up to 80% of healthy subjects showed no dysfunction (score 4) in any cervical movement, the only exception being lateral flexion (impaired in 47% of controls). On the other hand, 63–91% of WH patients showed a dysfunction ranging from 100% to 25% (score = 0–3), lateral flexion being the movement most frequently reduced (Table 5).

When WH patients were compared with an age-matched population (Table 5), a significantly reduced ROM was found in all movements ($P<0.05$ in right flexion-rotation and right rotation, $P<0.005$ in extension-rotation, flexion, left flexion-rotation, left lateral flexion and left rotation; Mann–Whitney *u*-test), in

Table 4 Intraclass correlation coefficient (ICC) values for cervical movements assessed by clinical examination to compare mean differences between the two examiners

Movement	ICC
Right flexion	0.68
Left flexion	0.68
Right extension-rotation	0.72
Left extension-rotation	0.72
Right flexion-rotation	0.86
Left flexion-rotation	0.86
Right lateral flexion	0.73
Left lateral flexion	0.47
Right rotation	0.77
Left rotation	0.78

Table 5 Clinical evaluation in whiplash patients ($n=70$) and in an aged matched population ($n=30$)

	Whiplash		Controls	
Movement	0–3	4	0–3	4
Right flexion (score)				
n	44	22	4	26
%	67	33	13	87
Left flexion				
n	44	22	4	26
%	67	33	13	87
Right extension-rotation				
n	46	20	6	24
%	70	30	20	80
Left extension-rotation				
n	46	20	6	24
%	70	30	20	80
Right flexion-rotation				
n	44	26	6	24
%	63	37	20	80
Left flexion-rotation				
n	50	20	6	24
%	71	29	20	80
Right lateral flexion				
n	62	6	14	16
%	91	9	47	53
Left lateral flexion				
n	60	8	14	16
%	88	12	47	53
Right rotation				
n	46	24	6	24
%	66	34	20	80
Left rotation				
n	50	20	6	24
%	71	29	20	80

For statistical significance see text.

particular in right lateral flexion ($P<0.001$). The significance of ROM impairment increased when matching WH patients vs. controls both with a decreased ROM (score 0–3) (Table 5).

Computing the number of ICMs, a significantly higher number was found in WH patients than in controls ($P<0.001$) (Table 6a). Since 74% of WH patients showed more than five reduced movements, and in 87% of controls four or less movements were reduced, we took impairment of more than five cervical movements as a reliable 'cut-off' point to distinguish reduced ROM (>5) from normal ROM (≤5) (Fig. 4). Moreover, the number of ICMs was significantly higher in WH patients with a recent whiplash injury (≤6 months) than in those with a longer illness duration (Table 6b), and when comparing T0 vs. T6 and vs. T12 (Fig. 5), a significant reduction in ICMs was found at T6 vs. T0 ($P<0.05$, ANOVA for repeated measures, Bonferroni's test) (Table 6c). In Table 7, the frequency and percentage of clinical dysfunction in patients with a recent whiplash injury (≤6 months) and in WH patients and longer illness duration (>6 months) are shown.

A higher percentage of recent whiplash injury subjects (77–100%) than patients with longer disease duration (50–86%) showed a reduced ROM, the most frequently reduced movements being extension-rotation, left flexion-rotation and lateral flexion (Table 7). Lateral flexion was also the most frequently reduced movement in WH sufferers with a longer disease duration. No significant differences were found at clinical evaluation of neck movement when comparing patients at T0, T6 and T12.

Patients with a whiplash occurring between 6 months and 1 year and those who had sustained a whiplash injury within the previous 6 months showed a significant clinical impairment of flexion-rotation and extension-rotation movements (respectively: $P<0.05$ and $P<0.001$,

Table 6 Number of impaired cervical movements (ICMs) on clinical evaluation

a. Number of ICMs on clinical evaluation in WH patients and in an age-matched population

	No. ICM, mean ± SD
WH patients	7.0 ± 3.0*
Controls	2.4 ± 2.8

*$P<0.001$; one-way ANOVA.

b. Number of ICMs on clinical evaluation in WH patients with a recent whiplash (≤6 months) and WH patients with a longer illness duration

	No. ICM, mean ± SD
WH ≤6 months	8.9 ± 1.8*
WH >6 months	5.9 ± 3.1

*$P<0.005$; Mann–Whitney test.

c. Number of ICMs at clinical evaluation in WH patients at T0 ($n=70$), T6 ($n=26$) and T12 ($n=12$)

WH	No. ICM, mean ± SD
T0	7.0 ± 3.0
T6	3.0 ± 4.2*
T12	1.1 ± 2.8

*$P<0.05$; ANOVA for repeated measures, Bonferroni test.

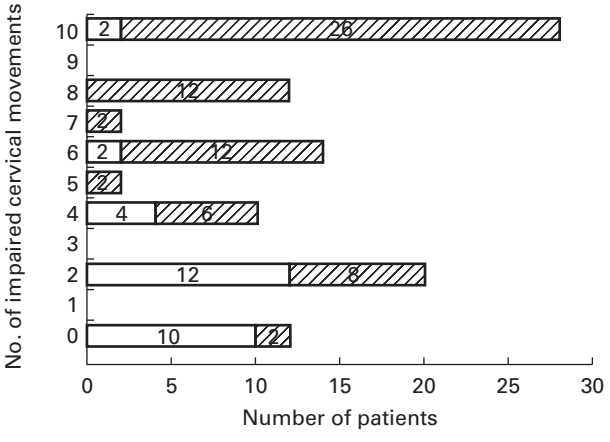

Figure 4 Number of impaired cervical movements (ICMs) in whiplash patients (WH) and in controls (Co). □, Co ($n=30$); hatched, WH ($n=70$).

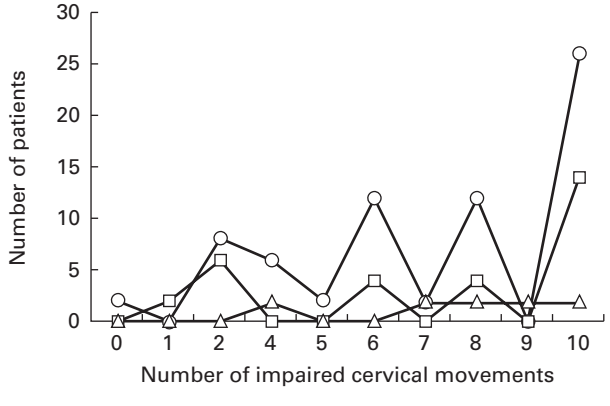

Figure 5 Number of impaired cervical movements in whiplash patients (WH) at time of first consultation, at 6-month (T6) and 12-month (T12) follow-up. ○, WH T0; □, WH T6; △, WH T12.

Table 7 Clinical evaluation in patients with a recent whiplash ($\leq$6 months) (n=26) and in those with a longer illness duration (>6 months) (n=44)

	Whiplash $\leq$6 months		Whiplash >6 months	
Movement	0–3	4	0–3	4
Right flexion (score)				
n	20	6	24	16
%	77	23	60	40
Left flexion				
n	20	6	24	16
%	77	23	60	40
Right extension-rotation				
n	26	0	20	20
%	100	0	50	50
Left extension-rotation				
n	26	0	20	20
%	100	0	50	50
Right flexion-rotation				
n	22	4	22	22
%	85	15	50	50
Left flexion-rotation				
n	26	0	24	20
%	100	0	55	45
Right lateral flexion				
n	26	0	36	6
%	100	0	86	14
Left lateral flexion				
n	24	4	36	6
%	92	8	86	14
Right rotation				
n	20	6	26	18
%	77	23	59	41
Left rotation				
n	22	4	28	16
%	85	15	64	36

Kruskal–Wallis test) when compared with subjects with a longer disease duration.

No significant differences emerged among WH patients when comparing clinical evaluation at T0 with T6 and T12 (Friedman's test), although a trend towards improvement was seen.

Discussion

Many different opto-electronic devices have been conceived to obtain non-invasive, three-dimensional dynamic measurements of neck mobility (17–20).

3D kinematic analysis allows cervical spine function to be investigated, detecting ROM impairment not only due to organic lesions, as in the case of simple X-rays, but also due to neck dysfunction.

Dynamic radiographs, in fact, although useful for examining kinematic function of the cervical spine, necessitate a considerably high and lengthy exposure to radiation, which increases as (in order to obtain a more detailed examination) the number of X-rays is increased.

Despite its sophisticated software, the Elite system is reliable and relatively easy to use (17). Based on a simplified kinematic model of the anatomical head–neck structure, it evaluates the head and trunk as two rigid bodies able to move freely in space, without the need to restrict the subject's movement. The direct acquisition of markers positioned over selected points and/or of the so-called 'technical markers' (see Methods) eliminates the errors associated with marker positioning and detection that occur during X-ray elaboration, in particular when two radiographic projections are superimposed, and homologous landmarks have to be detected in both of them (2). However, even in the case of 3D kinematic analysis, specific staff training is necessary and the equipment used is expensive. While it is true, however, that goniometers and inclinometers (5, 7, 9–13) are inexpensive, quick, easy to use, and can show an acceptable, and in some cases even good, level of reproducibility, the intervention of an experienced examiner is nevertheless needed to increase the accuracy of the measurement. Inclinometers, in particular, have been shown to have rather poor resolution (15°), and not to be good tools for follow-up evaluation over a long period of time (15).

The first device conceived by Roozmon et al. (19, 20), the Cervicoscope (a variation of the Spinescope, albeit improved by the addition of a display to describe coupled joint motion) (20), requires sophisticated software engineering techniques to present the required information to clinicians efficiently and accurately. In fact, while the Elite system evaluates the position of the anatomical segments by measuring the angle between the head and the laboratory co-ordinate system, the Cervicoscope software is based on the movement of vectors calculated from the 3D spatial co-ordinates of the infrared emitting diodes (IREDs) placed on the head, neck, and shoulders. This procedure is based on the development of three algorithms to deduce the relative direction angles between vectors normal to the different groups of IREDs and with respect to the absolute reference frame. Therefore, the method used in the present study extrapolates biomechanical parameters of real clinical relevance.

Moreover, the Elite kinematic model, based on the reconstruction of six anatomical points, is, unlike the one based on 3D facial morphometry applied by Ferrario et al. (17), able to supply a complete description of head/neck mobility. This latter method, in fact, using

the same digital image analyser, assessed alterations in the pattern of movement, calculating instantaneous centre of rotation and radius curvature only for flexion-extension movement, without considering lateral bending and rotation.

In contrast, the 3D anatomical model used in the present study made it possible to compute (in degrees of motion) the active cervical ROM for each movement evaluated, without any mechanical constraint, and, calculating velocity and acceleration of all visible markers, to obtain a more in-depth investigation.

A more complex 3D kinematic analysis method was used by Osterbauer et al. (18) in a relatively recent study, in which instantaneous helical axis (IHA) and a total biomechanical score were computed to characterize qualitatively movements of the head relative to the trunk. This method, based on a complex mathematical reconstruction of neck movements, describes alterations in the estimation of IHA during flexion-extension and oblique tracking tasks.

In our setting, all neck movements, with the exception of extension, were significantly reduced in whiplash patients. Osterbauer et al. (18), too, found a significant impairment of neck mobility in patients with whiplash injury. In order to find a biomechanical parameter that describes the total motion of the cervical spine, a GIM was calculated. This appeared to be useful as a first approach to neck impairment, as whiplash patients, compared with controls, showed a significantly reduced GIM, even though we were unable to detect any significant differences between patients grouped according to the WAD classification, between different types of headache or between patients at T6 and T12**.** These data seemed to agree with those obtained by Osterbauer et al. (18): the total biomechanical score computed in their study showed good sensitivity and specificity. It is worth noting that while we asked patients to perform three movements at a natural cadence, starting from their normal sitting position, the patients of Osterbauer et al. (18) were required to trace lines on the wall with a laser pointer; in fact, it is more difficult to measure (and interpret) biomechanical abnormalities occurring in the path of a set motion than those occurring during free movements based only on an individual 'movement scheme' (in other words, where there is no requirement to follow a predetermined trajectory).

Dvorak et al. (4) found hypermobility in the upper segments in patients with cervical trauma. As often occurs in whiplash injury, a muscular restraint can result in a decrease in the muscular force needed to limit motion at upper and middle cervical spine level where, because of the less stable gliding motion of the cervical spine at these levels, considerable muscular force is required. In the present study, in contrast, whiplash patients showed normal ROM as regards extension, while all the other movements were reduced as in hypomobility of the lower cervical spine, probably due to soft tissue damage and/or muscle restraint. Extension proved to be significantly impaired in patients with a recent whiplash injury ($\leq$6 months), improving in a shorter time than other neck movements.

Although clinical evaluation showed a globally acceptable level of interobserver reliability, only flexion-rotation and rotation movements gave good ICC values, while left lateral flexion was shown to be unreliable, probably due to an extreme intra- and interindividual variability in its amplitude or, possibly, to weakness towards the end of the examination, when lateral flexion was usually evaluated. Moreover, it has to be said that the amplitude of lateral flexion varies greatly from subject to subject and, without producing great discomfort, is reduced by age and by degenerative pathologies, such as arthrosis. Similarly, in a previous study by Fjellner et al. (27), six of the eight cervical movements clinically investigated by two experienced physiotherapists, in particular rotation, showed an acceptable level of reliability.

The 3D kinematic analysis, in contrast, showed a good–excellent reproducibility for all movements (21) and proved to be an objective method that is more reliable and sensitive than clinical examination. Nevertheless, clinical evaluation proved to be useful, as a basal screening, in distinguishing whiplash patients from asymptomatic controls.

Computing the number of ICMs, in order to select a 'clinical' biomechanical parameter that describes the total amount of neck motion, we noticed that 74% of patients showed impairment of more than five movements; whereas four or fewer movements were found to be reduced in 87% of controls. Thus, we took impairment of more than five cervical movements as a 'cut-off' point to distinguish neck dysfunction (with a reduced ROM) from normal cervical spine mobility. This 'cut-off' point, and the ICMs themselves, were shown to constitute a good and useful 'marker' of neck impairment, as revealed by the significant differences both between WH patients and controls and between patients with a recent whiplash injury and those with a longer respite since the whiplash. Furthermore, the ICMs, showing a trend towards decrease (i.e. towards improved ROM), also proved to be quite useful not only in the diagnosis, but also in the follow-up of cervical spine dysfunctions (in particular whiplash injury). In our setting extension-rotation, left flexion-rotation and lateral flexion were the movements most frequently impaired in patients with a recent whiplash injury (and lateral flexion the most frequently reduced also in those with a longer disease duration).

Moreover, flexion-rotation and extension-rotation were significantly reduced in patients with a recent whiplash injury ($\leq$1 year and $\leq$6 months), these two movements apparently being the most reliable and useful 'clinical markers', at 'first screening', for the diagnosis and follow-up of neck dysfunction. It should also be noted that lateral movements, such as flexion-rotation and rotation, showed good reproducibility (ICC values).

The results of clinical evaluation seem to show a marked agreement with those of 3D kinematic analysis, and clinical evaluation seems to be reliable as a first examination tool, identifying cases of neck dysfunction that have a high probability of being confirmed by an objective evaluation such as the 3D kinematic analysis. These results partially agree with those obtained in the study by Fjellner et al. (27), indicating a difference in reliability between symptomatic and asymptomatic subjects (greater in the former).

Moreover, as regards percent variation, whiplash patients showed a tendency towards an improvement in cervical ROM impairment over time. Thus, 3D kinematic analysis proved to be a useful tool for follow-up evaluations in neck disorders. The large SD recorded in flexion-extension movements when comparing T6 and T12 with T0 data are due to some patients showing, at T0, a strongly reduced ROM, which is increased two to three-fold at T6 and/or T12 follow-up. The relative high drop-out rate in our patient series may be due to the fact that cases with a clinical improvement and solved compensation claim may be less prone to undergo a new assessment of neck function. Further follow-up studies may reveal a higher sensitivity by analysing 3D methods with passive and active clinical evaluation.

In conclusion, the method for the 3D kinematic analysis of cervical movements used in this study proved to be reliable, easily applicable in difficult clinical cases and, most of all, useful in whiplash injury diagnosis and follow-up evaluation. Clinical evaluation, on the other hand, was shown to be useful as a 'first screening' tool correlating with data obtained using the 3D kinematic analysis method. However, the Elite system remains a 'sophisticated' method of spine movement evaluation, and due to its cost is not designed for routine use but mainly for difficult clinical cases in forensic medicine and for research purpose.

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Hemicrania continua: diagnostic criteria and nosologic status

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Proposals for the diagnostic criteria for hemicrania continua (HC) and also for the nosological status of HC are set forth. The clinical constellation of symptoms and signs making up HC consists of: unilaterality without side shift; absolute indomethacin effect; and long-lasting repetitive attacks of varying duration, eventually with a chronic pattern, the pain being mild to severe. For the typical clinical picture of HC, including a positive 'indotest', we propose the term hemicrania continua vera. More or less analogous, but 'indotest-negative' clinical pictures have provisionally been termed hemicrania generis incerti (of undetermined nature). At the present level of knowledge, the diagnosis of hemicrania generis incerti should be made mostly by exclusion. HC may possibly best be classified along with chronic paroxysmal hemicrania (CPH) as this is the only other headache absolutely responsive to indomethacin. The bond between these two headaches on the one hand and cluster headache on the other should, at most, be a loose one. Interrelationships of these four classifiable headaches are briefly discussed. □ *Hemicrania continua, hemicrania generis incerti, cluster headache, chronic paroxysmal hemicrania, indomethacin, unilateral headaches*

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Introduction

In the present communication, diagnostic criteria for hemicrania continua (HC) are proposed. Since the positioning of this headache in the classification has not been determined so far, our points of view regarding the nosological positioning of HC are also set forth.

HC was described as a syndrome in 1984 (1). On a world-wide basis, the number of HC cases increased to 18 during the next 5 years (2), whereas during the first 6 years after the description of chronic paroxysmal hemicrania (CPH) (3) only eight cases of CPH had been diagnosed. Nevertheless, this relatively small number of cases reported in the literature at the time may have been one reason for not including HC in the International Headache Society (IHS) classification system in 1988 (4). More recently, a clinical description of HC has been included in the International Association for the Study of Pain (IASP) classification (1994) (5). Fifteen years after the first report, a number of patients have been detected around the world (6, 7). Single cases of typical HC are not systematically published anymore; the real number of diagnosed cases probably is considerably higher than summing-up figures from the literature would indicate.

This headache category is still *sub judice*. Hemicrania continua does not seem to be a sub-fraction of the so-called chronic daily headache, as claimed by others (8). The reason for this statement is twofold. First, the unilaterality, the absolute response to indomethacin, and the occasional autonomic phenomena, should rather link this disorder to CPH. Secondly, a daily occurrence should not be sufficient for including this headache in the same category as other conditions with a pathophysiology distinct from that of HC. Hemicrania continua should probably be included in IHS group 3.

The diagnostic criteria

The criteria are presented in Table 1.

Table 1 Hemicrania continua: diagnostic criteria

A.	Headache for a total of $\geq$2 months
B.	Obligatory features
(I)	Unilaterality without side shift*
(II)	Absolute and protracted indomethacin effect†
(III)	Long-lasting, repetitive attacks – hours/days/weeks, with a tendency to a fluctuating chronic pattern over time‡
(IV)	Intensity of pain: mild, moderate or severe (not excruciatingly severe)
C.	Other non-obligatory but frequent characteristics of the pain syndrome
(I)	Female sex
D.	Negative provisos
(I)	Relative shortage of 'local' autonomic phenomena§
(II)	Relative lack of 'migraine' symptoms and signs¶
(III)	Relative lack of 'cervicogenic' symptoms and signs**
(IV)	Lack of effect of migraine and cluster headache drugs (triptans and ergotamine)

*The pain is mostly in the 'anterior' area, but not infrequently also in the auricular/occipital area. †Provided the dosage is adequate: 150 mg per day for 3 days. In the doubtful case, the 'indotest' should be carried out (see *Headache* 1998; 38:122–128). This is particularly important in the remitting cases, since a betterment of pain in reality being due to a remission may falsely be ascribed to indomethacin. ‡There are two forms of HC from a temporal point of view: a remitting and non-remitting (chronic) form. There may be transitions from the one temporal pattern to the other. The continuous pattern may eventually seem to dominate. §Lacrimation, conjunctival injection, rhinorrhea and nasal obstruction; such signs are usually meagre and on the symptomatic side, and, if present, they occur mostly during the more severe attack periods. ¶Nausea, vomiting, photo- and phonophobia, pulsatile character of pain and accentuation upon mild physical activity. **Reduction of range of motion in the neck; ipsilateral upper extremity discomfort; mechanical precipitation of pain/attacks.

The items under B (numbers I–IV) would seem to be more or less obligatory ones.

Item C I is non-obligatory; its presence nevertheless strengthens the diagnosis.

Each item under D (numbers I–IV) is non-obligatory, because of the 'relative' and not absolute character of each proviso. The reverse situation may present itself for each solitary negative proviso without violating the diagnosis (for instance autonomic features may be present, D I).

D III–IV possibly carry more weight than D I–II. If 'cervicogenic' symptoms and signs (D III) were present and marked, a diagnosis of HC alone would not necessarily be acceptable, even in the presence of an ample indomethacin-effect. Such cases should be reported separately to help upgrade future classification versions. D IV may possibly be an exception: one would hardly accept, for example, a complete triptan effect in HC.

A combination of the negative provisos may clearly favour a HC diagnosis.

Jabs or idiopathic stabbing headache are not mentioned among the criteria for HC. The reason for this is: although jabs appear not infrequently in HC, it is a highly unspecific phenomenon, appearing, for example, in migraine, tension-type headache, and also in headaches more similar to HC, such as cluster headache and CPH.

Classification

The possible link between HC and CPH

The nosological position of HC should reflect its clinical manifestations. HC belongs to the group of primary, strictly unilateral headaches. In addition, the striking response to indomethacin—a property common to HC and CPH—makes it reasonable to vent the idea of co-classifying HC with CPH. CPH is so far the only other headache absolutely responsive to indomethacin, a fact that, at this stage of insight, supposedly links such disorders. The strict unilaterality also strengthens the bond between them, and so does the clear female preponderance. It should be emphasized that both headaches also exhibit remitting and non-remitting clinical forms. The two headaches differ clearly as regards the following clinical variables: duration and degree of pain, and also the extent of autonomic involvement. Thorough search for additional, distinguishing traits between them has uncovered only minor—and mostly probably insignificant—differences (9).

Cluster headache and CPH

The similarity between HC and CPH by far exceeds that between CPH and cluster headache, where differences predominate (9, 10). The indomethacin response is a factor that crucially distinguishes cluster headache and CPH; the differing sex preponderance another; the prevalent temporal pattern a third; the lack of effect of 'cluster headache drugs' in CPH is a fourth, etc. Almost as important may be the abnormal sweating pattern demonstrated in the central part of the forehead on the symptomatic side in many cases of cluster headache, but not in CPH (11). These are actually decisive differences.

CPH was nevertheless provisionally categorized together with cluster headache (4). Whether this was a correct decision from a long-term perspective is open

to debate. If this practice is going to be be continued, then a clear line, in our estimation, should be drawn between the two (9,12). It is possible that 25 years after the description of CPH one may be facing an 'inverse' nosologic situation: that of unleashing the bonds to cluster headache. Clarity as to the relationship between cluster headache and CPH may also provide clarity as regards the nosological positioning of HC.

Hemicrania continua vera and Hemicrania generis incerti (of undetermined nature)

Just as in CPH, a positive indomethacin response is a fundamental property of HC. However, since the inception of HC, similar clinical pictures but unresponsive to indomethacin have been reported. It has been a matter of controversy whether such patients do suffer from an 'indomethacin-resistant' variety of HC, and the disagreement regarding this feature has been appreciable. Since no markers for HC are available, the actual relevant question is how HC may be diagnosed in the absence of an indomethacin effect. A hemicrania alone hardly suffices diagnostically. The nature of such a hemicrania with negative indomethacin response or where such response is untried remains most unclear; it may not belong to the HC cycle at all. Accordingly, we propose that the typical clinical picture of HC, including a positive 'indotest', be termed hemicrania continua vera. More or less analogous, but 'indotest-negative' clinical pictures can provisionally be termed hemicrania generis incerti (of undetermined nature).

The reponse to indomethacin was rather readily acknowledged as a diagnostic criterion of CPH. There has for instance been no temptation to consider cluster headache as an 'indomethacin-resistant CPH'.

A proposal for classification of HC

A proposal for the classification of HC in context with cluster headache and CPH is set forth in Table 2. A heavy line is inserted between on the one hand cluster headache and on the other HC vera and CPH. In the future, it may even be preferable to classify the two indomethacin-responsive headaches separately from cluster headache as the few dissimilarities that may seem to exist between them may be just apparent. Actually, the bond between CPH/HC and cervicogenic headache may be stronger than the bond between CPH/HC and cluster headache.

The advantages of provisionally considering HC vera and hemicrania generis incerti separately are obvious: (i) The clinicians will be less bothered by what are frequently experienced as cumbersome situations regarding response/non-response to indomethacin. (ii) The 'indotest' can be a useful procedure, enabling this clinical refinement. (iii) One can more conveniently share descriptions, also internationally, thus allowing further developments.

Table 2 Proposed classification of hemicrania continua and chronic paroxysmal hemicrania

Cluster headache
Chronic (non-remitting) form
Remitting form
Chronic paroxysmal hemicrania
Chronic (non-remitting) form
Remitting form
Hemicrania continua vera
Chronic (non-remitting) form
Remitting form*
Hemicrania generis incerti†

A heavy line is inserted between cluster headache and the two indomethacin-responsive headaches to show the clear alienation between them. *The extent to which HC vera will persist in the remitting form is not entirely known. †Provisional term. It could also probably be termed 'hemicrania of undetermined nature'.

As far as diagnostic criteria of HC (vera) are concerned, one should mainly rely on the positive provisos. Negative provisos may minimize any possible uncertainty. Fulfilment of the criteria would more or less seem to ascertain a HC vera diagnosis. Until the nature of Hemicrania generis incerti is known, diagnosis should be made mostly by exclusion. This is a provisional diagnostic category, in all probability subject to repeated revisions. A constant critical eye on this subgroup may solve the present confusion and clarify whether this is a variant of HC vera or, what is more likely, whether it qualifies as one or more independent categories of headache. An unravelling of the pathogenesis may provide us with the final word.

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REVIEW

The hemicrania continua diagnosis

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More than 16 years after the first description of hemicrania continua (HC), its aetiology and pathogenesis remain obscure. Clinically, HC is considered a syndrome with two pivotal characteristics: (i) strictly unilateral (moderate, fluctuating, relatively long-lasting) headache; and (ii) absolute response to indomethacin. HC is further characterized by some ancillary, but mostly 'negative', features such as: (iii) relative paucity of accompaniments; and (iv) lack of precipitating factors. The female preponderance is also remarkable, although not diagnostic in the solitary case. Finally, a non-specific, but remarkable feature is the temporal pattern. HC may present as a remitting or chronic (continuous) headache. In HC, unilaterality and absolute response to indomethacin are considered crucial diagnostically. Existing controversy, such as regarding atypical features, particularly the so-called 'HC resistant to indomethacin', is discussed. The nature of hemicrania with negative indomethacin response remains most unclear; it may not belong to the HC cycle at all. Accordingly, we propose that the typical clinical picture of HC, including an absolute response to indomethacin, be termed *Hemicrania continua vera*. More or less analogous, but indomethacin-resistant, clinical pictures can provisionally be termed *Hemicrania generis incerti* (of undetermined nature), provided other diagnostic possibilities have been ruled out. The differential diagnosis of HC vs. other unilateral headaches is commented on. Previous attempts at classification of HC into the group chronic daily headache (CDH) are discussed. The only acceptable 'link' of HC with the other headaches classified as CDH is the temporal pattern (which is a non-specific feature). HC is probably pathophysiologically different from the others disorders classified under CDH. Conversely, HC and chronic paroxysmal hemicrania share many common features, including the absolute response to indomethacin. HC should probably be included in the IHS group 3. □*Chronic paroxysmal hemicrania, cluster headache, hemicrania continua, hemicrania continua vera, hemicrania generis incerti, indomethacin, unilateral headaches*

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Introduction

Sixteen years after the first report of hemicrania continua (HC), a substantial number of patients have been detected around the world and several considerations regarding the clinical picture and diagnostic criteria (1–20) have been made. Attempts to classify HC have also been proposed (21, 22). However, neither the aetiology nor the pathogenesis of HC are known, which makes such attempts particularly difficult. For the time being, HC should be considered as a syndrome. In the absence of aetiopathogenic criteria, syndromes are classified according to the strategy of considering clinical features as probably revealing a common underlying malfunction and pathology. The set of characteristics, constantly present in a given disorder, are considered to

be interrelated and sharing a common pathogenic origin, and such symptoms and signs—*pecularia et perpetua phaenomena*—can be selected as diagnostic criteria. Differences in intensity, temporal pattern and association of non-specific features may give rise to the variants or even a spectrum.

A syndrome reflects a chain of physiological processes that, when interrupted, produces the same impairment of bodily functions (23). For obvious reasons, for a syndrome to be present, at least two specific clinical features must be present.

The syndrome HC presents two robust characteristics: (i) strict unilaterality of the pain (moderate, fluctuating, relatively long-lasting); and (ii) absolute response to indomethacin. These two features may reflect the most reliable characteristics of a syndrome: localization and pathogenesis. HC is further characterized by mostly 'negative' features, such as (iii) relative paucity of accompaniments; and (iv) lack of precipitating factors. Finally, non-specific, but remarkable features are the temporal patterns: either episodic or chronic, as happens in many (all?) headaches. If we follow the mandatory diagnostic hierarchy of characteristics, constant positive features should prevail over both negative and non-specific features. Atypical features may provisionally be accepted, provided they appear in patients exhibiting otherwise typical traits. Problem cases should be coded as non-classifiable cases until further insight is available.

The clinical picture

Unilaterality

Anatomically speaking, a strictly unilateral headache, as any other unilateral neurological symptom, is likely to originate from a lateralized lesion or dysfunction. HC is not just a unilateral headache, but a strictly unilateral one. Strictly unilateral means that only one—and always the same—side is symptomatic. From a conceptual point of view, this is absolutely different from unilateral but shifting sides headaches, i.e. disorders in which the pain may arise from either side. In bilateral or holocranial headaches, both sides are synchronously and rather symmetrically affected. Neither headaches shifting sides nor bilateral headaches, in principle, qualify for a diagnosis of HC, as in the absence of a clarification of the pathogenetic mechanisms of this headache, atypical features *per se* cannot be accepted as belonging to the diagnostic criteria. Regarding localization, one can only accept atypical features, i.e. side shift or bilaterality, when the remaining signs and symptoms are typical, and when other headaches have been ruled out. Even when these conditions are met a diagnosis of HC should be made only with considerable reservations. The demands as to the interpretation of the response to indomethacin (see later) will have to be strict in such cases. Only one new sign, or symptom, should be allowed at a time and then still with a question mark until either more reports substantiate such a new finding or the unravelling of pathogenesis and aetiology finally confirm the clinical picture.

Response to indomethacin

HC patients respond dramatically, within 24 h and many in less than 8 h, to a standard oral dose of indomethacin (24). If administered intramuscularly, the response should be expected within 1–2 h (25). The latter trial is the ideal one in the diagnostically problematic case, chiefly because of the quick and clear response. What makes this pharmacological response so unique is that HC uniformly responds to only one drug, indomethacin. Virtually all NSAIDs have been tried in HC and—in equipotent doses—not one showed the extraordinary effect provided by indomethacin. Therapeutic alternatives in patients with intolerance to indomethacin may include aspirine (1–4, 11), piroxicam (26, 27), ibuprofen (28) and rofecoxib (29).

Indomethacin provides a complete response, provided the dosage is titrated, and there does not seem to be any tachyphylaxis, and a substantial reduction of the dose may be expected in time (30). Typical fluctuation of pain exists, and patients need to modify the dose accordingly, dosages ranging between 25 mg every 2 days and 250 mg daily. Even if one is faced with a headache that in principle is indomethacin-responsive, the untoward effects of the high dosage may hinder an optimal trial of indomethacin. Moreover, the persistent requirement of high indomethacin doses may indicate the presence of a symptomatic form (31, 32).

Indomethacin provides only a remission, not a cure. Withdrawal of medication generally allows the symptoms to reappear after a variable latency provided the patient has reached the continuous phase. After discontinuation of indomethacin a relatively long-lasting symptom-free period has been observed in three patients, the mean follow-up time being reported as 13 months (33).

Indomethacin response as a diagnostic criterion

If a treatment interrupts the chain of pathogenic events, it should be regarded as a crucial specific agent. If, in addition, there is only one effective drug it should be classified as extreme selectivity. Taking these properties together, they are reminiscent of what one can expect from antidotes. The selective sensitivity and superb response point towards considering indomethacin as a rather specific drug that probably reaches the core

of the pathogenetic mechanisms of HC. HC shares this sensitivity to indomethacin with only one other headache: chronic paroxysmal hemicrania (CPH).

Cases with lack of response to indomethacin ('indomethacin-resistant' cases) have been described (16, 17). From another perspective, only a successful trial with indomethacin allows a diagnosis of HC. Only HC and CPH (34, 35) are absolutely responsive to indomethacin. This rather unique drug effect has therefore been included in the syndrome definition itself as regards both CPH and HC.

It has been proposed to consider indomethacin responsiveness as a confirmatory trait (36), instead of a *sine qua non* diagnostic criterion. This proposal at face value might seem to alleviate the discomfort of having to rely upon a pharmacological response as a diagnostic criterion. However, this introduces the possibility of a non-confirmed hemicrania continua, which increases diagnosis uncertainties. The attempt to develop diagnostic criteria for HC that would require either absolute indomethacin responsiveness or associated autonomic features (at least one) during exacerbations (36) may be not operative in HC. One reason for this is that the autonomic features are meagre and proper autonomic signs and symptoms may even not have occurred by the time the patient presents herself.

The pharmacological response should be considered diagnostic only when the test has been conducted in an optimal way. With a negative indotest the actual disorder would be at variance with HC and other diagnostic possibilities should be explored (37–41; Table 1). With a negative indotest, continuous indomethacin therapy is not indicated. Even when 'direct' diagnostic tools eventually become available, in HC it may be hard to skip this test.

Alleviation of the pain by some manoeuvres or therapeutic approaches is classically considered among the characteristics of various syndromes and in particular in some painful conditions. The response to treatment is actually—and wisely—acknowledged by the current IHS classification of headaches and cranial neuralgias (37) as diagnostic criteria for several conditions such as: (i) CPH, the other headache absolutely responsive to indomethacin; (ii) Tolosa–Hunt syndrome, 'pain is relieved within 72 h after initiation of corticosteroid therapy'; (iii) retropharyngeal tendinitis, 'alleviation within 2 weeks of treatment with nonsteroidal anti-inflamatory drugs in recommended doses'; and (iv) giant cell arteritis, 'disappearance of headache within 48 h of steroid therapy'. If this pharmacological attribute were to be removed, could it then be replaced by another, more specific or relevant criterion? The answer is 'no', or—to put it more correctly—'not yet'.

In other neurological disorders positive pharmacological responses are required for a better diagnosis. This includes the Tensilon test in myasthenia gravis, dopa-responsive dystonias, or an urgent flumenazil trial whenever a benzodiazepine overdose coma is suspected. The use of a pharmacological criterion in these disorders is not widely different from the classic procedure in which the final diagnosis of a given condition must await the expected results of the treatment and course (42).

Other primary headaches may respond promptly to drugs, but with marked variability both intra- and inter-individually. In contrast to what is the case with HC, this rather heterogeneous, pharmacological response prevents the use of pharmacological tests in the diagnosis of such headaches. As generally the clinical pictures are typical enough in these headaches, adherence to drug test is by no means obligatory.

How can the 'indomethacin-response dilemma' be clarified?

Unilaterality and prompt and absolute response to indomethacin are *insignis morbi* of HC. Ancillary features, such as moderate, relatively long-lasting pain, lack of precipitating stimuli, paucity of accompanying phenomena, and temporal patterns, are clinically useful provided the two crucial features are present. Accordingly, we have recently proposed (43) that the typical clinical picture of hemicrania continua, i.e. including an absolute response to indomethacin, be termed hemicrania continua vera. More or less analogous but 'indomethacin-resistant' clinical pictures are—by definition of the syndrome—different from HC and can be termed hemicrania generis incerti, provided other possibilities (see Table 1) have been ruled out. Moreover, both headaches according to the proposal could be classified along with cluster headache and CPH (43). The proposed nosologic frame for these strictly unilateral primary headaches is represented in Figure 1. It illustrates how the so-called 'indomethacin resistant HC' cases should be considered apart from HC. The same has been

Table 1 Strictly unilateral, primary, headaches with some resemblance to hemicrania continua

Supraorbital neuralgia
Cervicogenic headache
Strictly unilateral migraine
Post-traumatic dysautonomic cephalalgia of Vijayan and Dreifuss
Unilateral tension type headache
Atypical facial pain
Temporomandibular joint disorders

All these headaches are predominant in the female, strictly unilateral, may lack accompaniments, may exhibit a chronic or remitting pattern, and are resistant to indomethacin.

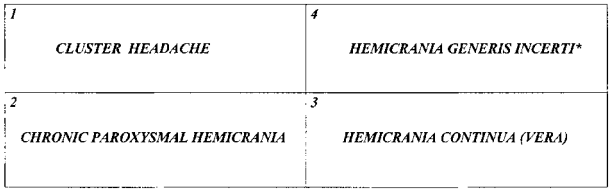

Figure 1 Proposed nosologic position of hemicrania continua. We have graphically represented cluster headache, CPH, HC vera and hemicrania generis incerti. The categorization principle is: primary strictly unilateral headaches. The nosological requirements: distinction, grouping, and gradation, have all been achieved. Indeed, the arrangement of the figure shows the relationships between these strictly unilateral primary headaches. On the left (1+2): the two relatively short-lasting, excruciatingly severe headaches, associated with marked autonomic features. On the right (3+4): the two relatively long-lasting, moderately severe, 'autonomically modest' headaches. At the bottom (2+3): the two headaches absolutely responsive to indomethacin. At the top (1+4): the two headaches non-responsive to indomethacin.
*Provided other diagnostic alternatives (see text and Table 1) have been ruled out.

acknowledged in CPH in its differentiation from cluster headache, which has never been considered as 'indomethacin-resistant CPH'. With regard to indomethacin responsiveness, hemicrania generis incerti is as different from hemicrania continua vera as cluster headache is different from CPH.

Paucity of accompaniments and lack of precipitanting mechanisms

During exacerbations, patients occasionally report that pain may be accompanied by a variable combination of ipsilateral, autonomic features such as conjunctival injection, lacrimation, photo- and phonophobia, ocular discomfort and nasal stuffiness (1–4, 11). When present, all these accompaniments seem to have a modest dimension, at least as compared with other unilateral headaches, such as CPH and cluster headache (11). Nausea may be present, but vomiting is not typical of this headache. In the largest series of HC (44), accompaniments were noticeable only during exacerbations. Less than one-third of the patients exhibited conjunctival injection, nasal stuffiness, rhinorrhea or ptosis, whereas lacrimation nausea, photophobia and phonophobia were found in *c.* half the patients.

Precipitating mechanisms—at least noticeable ones—are as a rule lacking in HC. More specifically, precipitants that are operative in other headaches generally seem to be of little relevance in HC (11); this goes for stress, menses, alcohol, vasodilators, or exteroceptive stimuli acting on the tissues supplied by the trigeminal nerve. Furthermore, the headache is not aggravated by the supine position (like cluster headache) or other positions, Valsalva manoeuvre, physical activity and—above all—neck movements (like cervicogenic headache and some cases of CPH) (45). Of course, it is unwarranted, or rather illusory, to consider the absence of certain characteristics as an intrinsic quality of a given condition. Negative features should be considered in the appropriate context which may or may not enhance the importance of the negative features.

Temporal patterns

This is an important but non-specific feature. In fact, many headache categories may exhibit both episodic and chronic patterns, but the crucial symptoms remain the same. HC may present with two temporal patterns: a remitting (non-continuous) and a chronic (continuous) pattern (1–4, 11, 12, 44). Putatively, patients may start their symptoms with either temporal pattern and remain in the same stage indefinitely without transition to the other stage. However, a frequent development is that the remitting pattern precedes the chronic stage. Such transition has frequently been reported by chronic HC patients. Documented transition from the remitting to the chronic stage has also been reported (46). The reverse temporal development, i.e. from the chronic to the remitting form, has rarely been observed after successful treatment with indomethacin (47). It is worthy of note that in patients with documented transitions between stages, indomethacin provided an absolute improvement whatever the stage was (46, 47). This supports the notion that HC is a single syndrome, presenting with two different temporal patterns.

HC has been proposed as a category of 'chronic daily headache' (CDH) based on its eventually continuous pattern (22). The only acceptable 'link' of HC with the other headaches classified as CDH is the temporal pattern: HC may present with daily symptoms in the same way as many other headaches and a myriad of disorders. However, as already mentioned, temporal patterns are non-specific. CDH is an expression that stresses the way a certain number of primary headaches may occur, and does not represent a distinct nosological entity. Therefore, CDH does not seem to be a satisfactory final diagnosis, but rather an explanation of how a headache manifests chronically in a certain patient. For the future, HC would probably be better classified together with CPH (IHS group 3), as an indomethacin-responsive headache (43, Figure 1).

Analgesics and other useful drugs that are employed in painful syndromes may modify both pain and accompaniments. However, there is ample reason to believe that a given disorder can not be transformed into an essentially different one through the medication, e.g.

treatment, because each disease has a distinctive aetiology and pathogenesis, the nature of which cannot be changed by treatment. A modified condition, however, is a change in the form or appearance of the original condition. Changes in symptom intensity or in the temporal pattern give rise to clinical variants, but never to another entity. Therefore, a 'transformed' or 'chronified' migraine is still a migraine, and a chronic or episodic tension-type headache are both tension-type headaches. Thus, a particular manifestation of a disease, drug-induced or not, must not be upgraded to a new diagnostic label. A patient with a certain headache disorder that changes with time cannot be classified twice: once under primary headaches and thereafter under CDH.

Admittedly, analgesic abuse may modify a given headache, giving rise to a chronic, daily pattern. HC is also usually characterized by chronic daily pain. The chronic use of indomethacin obviously does not produce another headache (CDH). Indomethacin has by now been given for >25 years in some cases without producing persistent headache, as demonstrated in CPH (see 46). The headache that appears on drug discontinuation of indomethacin is the original unilateral headache, with the unilateral accompaniments. It has, nevertheless, recently been argued that analgesic abuse is associated with HC (18). As HC is absolutely and permanently responsive to indomethacin, the main reason for HC sufferers to abuse analgesics and other medications is obviously the lack of appropriate diagnosis and treatment, or intolerance to indomethacin. Moreover, if a given patient suffering from HC abuses medication, which has been the case in many undiagnosed HC sufferers, the symptoms cannot be abolished unless indomethacin is administered. Otherwise, if indomethacin is discontinued, the symptoms will reappear sooner or later and will only be relieved upon resuming indomethacin medication. It is acknowledged that in order to consider a headache as directly related to medication abuse it is necessary to verify that symptoms first improve, and later more or less disappear after withdrawal of medication. HC behaves precisely inversely, provided it has been correctly diagnosed and treated. In a reported case of HC evolved from analgesic rebound (19), the patient was never even prescribed indomethacin. The positive effect of this drug should be regarded as an obligatory criterion for the diagnosis of HC.

CDH sufferers not only are suffering from a headache, but somehow contribute to the making of the headache themselves. In addition to a pre-morbid constitution, several symptom-producing habits, such as analgesic abuse, exposure to stressors, and various other circumstances, contribute to the final course of their headaches. Contrary to what is the case in HC, the patho-biography is probably crucial in understanding CDH.

Supplementary studies and research

In our experience, the exploration of forehead sweating (48), pupillometry (49) and pain pressure threshold (50) has not yielded any evidence of gross impairment in HC. The same trend was observed using pericranial nerve blockade (51) and sumatriptan administration (52). Only one single patient with an abnormal unilateral phlebographic pattern has been described so far (53). In the routine work-up, these tests do not seem to distinguish between HC and other unilateral headaches.

MRI of the brain failed to demonstrate gross pathological changes (53). However, at the present stage of knowledge, considering the possibility of the HC-like pictures (31, 32), one should at least be highly aware of two potentially dangerous situations: (i) continuously high indomethacin requirement; and (ii) decreasing indomethacin effect. The conclusion to be drawn from these situations seems to be that even though the clinical history might fit with a picture of 'primary' HC, it may be necessary to carry out a CT-scan and/or MRI of the brain in such patients until such time as other confirmatory tests are available for HC.

Conclusions

'Nothing more practical than a good theory' said L. Boltzmann. The term 'vera' (i.e. hemicrania continua vera) is in our opinion the best term for the genuine form of HC. Hemicrania generis incerti is a provisional concept. Headache phenotypes like this brand may provide us with higher insight into this field. In the foreseeable future, we may be in the position to ascertain whether hemicrania generis incerti is a variant of hemicrania continua or—what is more likely—another disorder. We believe that the postulated nosology may end the present period of controversy and bewilderment.

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Cervicogenic headache: evaluation of the original diagnostic criteria

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A variety of headaches are frequently associated with the occurrence of neck pain. The purpose of this paper was to describe the adherence to diagnostic criteria of a series of patients enrolled on the basis of two clinical criteria: (1) unilateral headache without side-shift, and (2) pain starting in the neck and spreading to the fronto-ocular area. One hundred and thirty-two patients (36 male and 96 female) entered the study. Sixty-two patients were assigned to Group A (patients fulfilling criteria 1 and 2), 40 to Group B (criterion 2 only) and 12 to Group C (criterion 1, only). Eighteen subjects were excluded because X-rays of the neck were not available. Patients were evaluated regardless of whether or not they fell into one or more of the following diagnostic categories: cervicogenic headache (CEH), migraine without aura (M) and headache associated with disorders of the neck (HN) (IHS definitions). Fulfilment of the diagnostic criteria for CEH was found to be particularly frequent in Group A. A higher frequency of CEH diagnosis was found when two criteria were used (Group A) than in Group B ($P = 0.001$); in the former group a higher mean number of diagnostic criteria for CEH were also present ($P = 0.001$). Group A patients more frequently presented pain episodes of varying duration or fluctuating, continuous pain and moderate, non-excruciating, non-throbbing pain than Group B patients ($P = 0.04$ and $P = 0.08$, respectively). In Group C patients, the frequency of these two criteria was relatively low (17%) especially of the first mentioned variable. The presence of at least five of the seven 'pooled' CEH criteria (present in $\geq$ 50% of the patients) might be deemed a reliable cut-off point, allowing the headache to be diagnosed as 'probable' CEH. If patients fulfilling M or HN criteria in addition to the CEH criteria are added to the 'pure' CEH group a total of 74% of Group A patients may have a CEH picture. The temporal pattern of pain and the quality of pain in Group A showed good sensitivity and specificity ($\geq$75) when compared with Group B; therefore, the chances of diagnosing a definite CEH are significantly more frequent in patients presenting with unilateral pain that also begins as a neck pain. Head/neck trauma and radiological abnormalities in the cervical spine were not significantly associated with CEH, M or HN diagnoses. An improvement of the current diagnostic IHS criteria might make it possible to avoid the existing, partial overlap of CEH with HN and M. Extensive use should be made of the GON, and other, blockades in the routine work-up of CEH, both in the differential diagnosis and in the mixed forms (CEH + M, and CEH + HN), in order to improve the efficiency of the current diagnostic system. □ *Cervicogenic headache, diagnostic criteria, migraine, neck*

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Introduction

Cervicogenic headache (CEH), as it was described in 1983 (1), is regarded as a preferentially unilateral headache that initially may be remitting but that tends to become chronic over time. It is of moderate intensity, appears most frequently in females, and is associated with symptoms and signs linking it to the neck. These include: onset of pain attacks in the neck/back of the head; reduced range of motion in the neck; precipitation mechanisms related to the neck, and possibly, the presence of shoulder/arm pain ipsilaterally to the head pain. A detailed clinical description of this headache appears in the IASP classification of chronic pain (2), where it is coded VII-2.

The clinical description of CEH as it appears in the original paper (1), is based on a relatively limited series. Clinical/instrumental evaluation provided evidence that the headache symptoms were the effect of a 'noxa', localized in the neck. Since then, this description has remained the point of reference for scientific purposes, i.e. further investigations of mechanisms, of levels of cervical dysfunction, and of treatments. However, the original criteria for CEH may have been rather specific, and thus their sensitivity could be unduly low. Some series of headache patients (retrospective evaluations) have pointed to such a trend (3). Attempts have been made to evaluate the consistency of the criteria for CEH in various series of headache patients (4–7). Fifteen per cent of the headache patients in an outpatient clinic in Brazil were identified as CEH (4, 5). In a Danish study (8), based on 826 randomly selected individuals from a population register, *c*. 18% were diagnosed as CEH cases. In Pereira Monteiro's study (6) of a population from Porto, the prevalence of CEH was found to be 0.4%, on the basis of the IHS criteria for headache associated with neck disorders. When the criteria of Sjaastad et al. (9) were applied, this prevalence rose to 1% and 4.6%, respectively, depending upon whether all, or only five, of these criteria were used. These data point to a higher sensitivity of the CEH criteria compared with the IHS criteria.

As described in the IHS diagnostic criteria in 1988 (10), the term 'headache associated with disorders of the neck' is clearly non-specific. Neck pain is also considered by the IHS classification to be the cause of referred headache or projected pain. The loose description 'headache associated with disorders of the neck' fails to specify, for example, the side, character and temporal pattern of the pain. It also requires X-ray evidence of changes in the neck (features which are not a regular part of the CEH definition). The IHS definition considers different pain conditions (tension-type headache, migraine, temporomandibular dysfunction, 'pure neck ache alone', etc.) to be fully acceptable for inclusion under the heading 'headache associated with disorders of the neck'. Furthermore, there exists no clinical study prior to 1988 conducted on a large clinical patient series that supports the consistency of the IHS criteria (of group 11.2.1), in particular the X-ray criterion, nor has any validation study of clinical/radiological criteria been carried out since the classification was proposed. On the other hand, the situation as regards CEH looks somewhat different: CEH, a secondary headache with a rather well-defined clinical picture, is characterized by two essential, clinical aspects: (a) unilaterality of pain; (b) a clinically demonstrable neck factor.

On a more general level, the IHS system and its diagnostic criteria display a reasonably good power of resolution if one considers episodic headaches (migraine, cluster headache) and neuralgias (11,12), but only few studies document their validity in more or less continuous forms. One flaw of the IHS system is its poor definition and importance of headache as a symptom among the secondary forms (i.e. 'associated with'), whenever a headache case is observed for clinical as well as epidemiological purposes.

Any investigation into CEH, be it clinical or epidemiological, will inevitably involve the need to consider diagnoses other than CEH, reached by applying standard diagnostic criteria, such as the IHS ones. There is thus the chance that CEH will find itself grouped with the IHS classification's 'unclassifiable' primary/secondary headaches, or (more frequently?) with the same classification's diagnoses of 'genuine' migraine, tension-type headache, headache associated with disorders of the neck, etc. (or even with more than one of the aforementioned diagnoses).

In order routinely to identify a headache as CEH, a category of 'possible CEH' cases is needed, but in order to develop such a category, the sensitivity and specificity of the diagnostic criteria would first have to be evaluated.

Currently, while the differential diagnosis of CEH vs. other unilateral headaches such as cluster headache (13), chronic paroxysmal hemicrania (14) and hemicrania continua (15) can be made with reasonable certainty, the greatest difficulties appear to concern the overlap between the respective diagnostic criteria for CEH and migraine without aura ('common migraine').

The principal aim of the present investigation was to ascertain the extent to which the following two complaints may assist in the classification of cases of 'possible' CEH: (a) pain starting in the neck and spreading to the frontal area; and (b) unilaterality of headache without side-shift.

We intend subsequently to evaluate the reliability of the CEH diagnosis (according to the original criteria) in a prospective series of patients.

Materials and methods

Patient series

The study was conducted on 132 consecutive patients (36 men and 96 women, mean age 35 ± 11 years; range: 19–70) educated for a mean of 12 ± 4 years. The mean age at headache onset was 29 ± 13 years; the mean illness duration was 6 ± 3 years, range 2.5–9 years.

Methods

Clinical information was obtained from patients at the time of their first consultation at the Headache Centre of the C. Mondino Foundation, University of Pavia. A headache history was obtained through a structured interview (part of the compilation of a large data base which also included standard clinical examination and the gathering of data relating to different instrumental, diagnostic and therapeutic procedures) conducted by a single investigator (FA). Patients were selected on the basis of two clinical characteristics derived from the original diagnostic criteria for CEH (1, see Appendix 1): (a) unilateral headache without side-shift; and (b) pain starting in the neck and spreading to the fronto-ocular area. They were then grouped as follows. Group A (presence of both features): unilateral headache without side-shift (I) and pain starting in the neck, eventually spreading to oculo-fronto-temporal areas, where the maximum pain is often located (VI). Group B (fulfilment of one criterion): pain starting in the neck, eventually spreading to the oculo-fronto-temporal areas (where the maximum pain is often located) (VI). Group C (fulfilment of one criterion): unilateral headache without side-shift (I). In group A and B, the neck pain was invariably unilateral at onset, but could eventually spread across the midline during particularly severe and protracted attacks.

Cluster headache and tension type headache were excluded on the basis of the diagnostic criteria established by the IHS in 1988 (10). Chronic paroxysmal hemicrania, and hemicrania continua were thought to be unlikely alternatives (2), but as far as the latter is concerned it should be emphasized that no formal indomethacin test was carried out (16), for which reason this diagnostic alternative cannot be completely excluded.

At a later stage, the diagnostic criteria for CEH (9), migraine (M) (10) and headache associated with disorders of neck (HN) (10) were assessed on the basis of a detailed work-up.

The original diagnostic criteria for CEH (9) were 'pooled', as shown in Table 1. They were then identified and counted in the single patient. This was done in order to assess the number of criteria needed for a headache stemming from the neck to be diagnosed as CEH.

X-rays of the cervical spine were carried out in order to evaluate an abnormal posture or flexion-extension impairment. In case of reduction of intervertebral space, patients underwent a preliminary CT scan, in order to evidence a disc protrusion/herniation, and eventually a spine MRI.

In most of the patients a proper GON anaesthetic blockade was not carried out, the pain being less than 50% of the maximum at the time of consultation.

Table 1 Pooled form (1–7) of the diagnostic criteria for cervicogenic headache proposed by Sjaastad et al. (1990); in each case the number of the original diagnostic criteria is given in brackets

(1)	Unilateral headache without side shift (I).
(2)	Symptoms and signs of neck involvement: (a) pain triggered by neck movement and/or sustained awkward position (IIa1) and/or external pressure over the ipsilateral upper, posterior neck or occipital region (IIa2); (b) ipsilateral neck, shoulder and arm pain of a rather vague, non-radicular nature (IIb); (c) reduced range of motion in the cervical spine (IIc).
(3)	Pain episodes of varying duration or fluctuating, continuous pain (IV).
(4)	Moderate, non-excruciating pain, usually of a non-throbbing nature (V).
(5)	Pain starting in the neck, eventually spreading to oculo-fronto-temporal areas, where the maximum pain is often located (VI).
(6)	(a) Anaesthetic blockades of the major occipital nerve and/or the C2 root or other appropriate blockades on the symptomatic side abolish the pain transiently, provided complete anaesthesia is obtained (VII)
or	(b) sustained a whiplash (neck trauma) a relatively short time prior to the onset* (IX).
(7)	Various attack-related phenomena: autonomic symptoms and signs, nausea, vomiting (Xa-Xb), ipsilateral oedema, and flushing mostly in the periocular area; dizziness (XI); photo- and phonophobia (XII); blurred vision on the eye ipsilateral to the pain (XIII).

*Criterion 6 embraces two criteria, namely (a) and (b); these two criteria were 'pooled' after the enrolment of the patients due to the lack of pain, in some of them, at the time of interview, and thus it was impossible to carry out a nerve blockade So, in this context, the fulfilment of one criterion suffices.

Statistical analysis

Data were analysed using the statistical program SPSS 6.3 for Windows. The chi-square (according to the one-tail Fisher's exact test correction) was employed to compare the single items making up the diagnostic criteria. ANOVA was used for comparing the total number of criteria for CEH present in the different groups.

Sensitivity and specificity of the diagnostic criteria were also calculated considering, respectively, patients presenting a symptom included in the diagnostic criteria (sensitivity), and patients not presenting an appropriate symptom and who thus did not satisfy the criteria (specificity).

Results

With reference to our inclusion criteria, 65.2% of the patients (86/132) had a unilateral headache (I) and in 87.9% ($n=116$), the pain started in the neck (VI). Eighteen patients (Group A = 8, Group B = 6 and Group C = 4) were not included in the final evaluation because cervical spine X-rays were not available. Therefore, the results relate to 114 patients: Group A (I + VI), 62 (54.4%); Group B (VI), 40 (35.1%); and Group C (I), 12 (10.5%).

Table 2 shows the relative frequency of the diagnostic criteria for CEH in patients belonging to Groups A, B and C, respectively (9).

Major symptoms and signs

Pain was induced by neck movements and/or sustained awkward head positioning, or by external pressure (II-a-1 and II-a-2) in 52% of the patients in Group A, in 40% in Group B and in 50% in Group C. Neck pain spreading to shoulder and arm ipsilaterally (II-b) was present as a rather vague, non-radicular pain in one-third to one-half of the patients (Table 2). The range of motion in the cervical spine was clinically reduced (at least 25% reduction in one or more passive movements of the neck) in a high percentage of patients (Group A = 84%, Group B = 80%, Group C = 67%) (II-c). No statistically significant differences emerged between the reported data recorded in the three groups of patients.

Pain characteristics

The pattern of the pain episodes in the three groups of patients was non-clustering; pain episodes of varying duration, or fluctuating continuous pain, was present in 62% of patients in Group A vs. 40% in Group B ($P=0.04$, two-sided Fisher's exact test) and 17% in Group C (Table 2). Pain was moderate, non-excruciating, usually of a non-throbbing nature, in 73% of the patients belonging to Group A vs. 55% in Group B ($P=0.08$, two-sided Fisher's exact test) and 50% in Group C (Table 2).

Other important criteria

Of the Group A cases in whom the procedure was carried out, the anaesthetic blockade of the GON was positive in only 17% (4/24). (Negative blockades: 20/24 in Group A; 18/18 in Group B and 8/8 in Group C). In 64 patients, anaesthetic blockade was not carried out, the pain being less than 50% of the maximum at the time of consultation.

A history of neck trauma, of the whiplash type, sustained prior to the pain onset was present in a relevant number of patients (Table 2).

Various attack-related phenomena

In the present series of patients, the minor (and more rarely occurring) diagnostic criteria were fulfilled in more than one-third of the patients (Table 2) only as regards dizziness in groups B-C.

Diagnostic criteria

Table 3 shows the relative frequency of the diagnoses CEH, M, HN (see Methods) when the diagnostic criteria are applied to the three groups of patients. A higher frequency of CEH diagnosis was found in Group A compared with Group B (respectively: 55% vs. 20%; $P<0.001$, Fisher's exact test) as one should expect from the hypothesis. It is also remarkable that no patients in Group A had a HN diagnosis, while in Group B 25% of the patients fulfilled the criteria for HN. The distribution of patients with diagnoses of CEH associated with M or HN is not statistically different in Groups A and B. Moreover, the number of non-classifiable patients is relatively higher in Group C than in patients in Groups A and B. No patient in any of the three groups presented a diagnostic overlap between M and HN.

Taking the seven 'pooled' diagnostic criteria for CEH (see Methods and Table 1), 74% ($n=46$) of the patients in Group A (including also CEH + M and CEH + HN patients) fulfilled at least five of them (three criteria in addition to the two obligatory criteria) compared with 35% ($n=14$) of the Group B (Group A vs. Group B $P=0.0028$, chi-square) and 17% ($n=2$) of the Group C patients (Group A and B vs. Group C $P=0.000$, chi-square) (Fig. 1). Fulfilment of at least five of the seven criteria seems to constitute a reliable cut-off point at which headache patients can be diagnosed as CEH, provided the head pain is unilateral and is starting in the neck ('possible' CEH).

Table 2 Relative frequency of diagnostic criteria for cervicogenic headache in patients belonging to Groups A, B and C

		Group A ($n=62$)		Group B ($n=40$)		Group C ($n=12$)	
Diagnostic criterion		*n*	%	*n*	%	*n*	%
Major symptoms and signs							
I.	Unilateral headache	62	100	–	–	12	100
II-a-1.	Pain triggered by neck movements and/or sustained awkward head positioning	24	39	14	35	4	33
II-a-2.	Pain elicited by external pressure over the GON or the ipsilateral upper, posterior neck region C2-C3‡	8	19	2	5	2	17
II-b.	Ipsilateral neck, shoulder and arm pain of a rather vague, non-radicular nature	32	52	14	35	4	33
II-c.	Reduced range of motion in the cervical spine	52	84	32	80	8	67
Pain characteristics							
IV.	Pain episodes of varying duration or fluctuating continuous pain	38	62*	16	40	2	17
V.	Moderate, non-excruciating pain, usually of a non-throbbing nature	44	73	22	55	6	50
VI.	Pain starting in the neck, eventually spreading to oculo-fronto-temporal areas	62	100	40	100	–	–
Other important criteria							
VII.	Anaesthetic blockades of the GON or C2 root	4	17†	0	0	0	0
IX.	Sustained neck trauma a relatively short time prior to the onset	32	52	30	75	8	67
Minor, more rarely occurring, non-obligatory symptoms and signs							
Xa-b. and XII	Rarely, nausea, vomiting, photo-and phonophobia	24	39	12	30	0	0
Xc.	Ipsilateral oedema and, less frequently, flushing, mostly in the periocular area	6	10	2	5	2	17
XI.	Dizziness	16	26	8	40	8	67
XIII.	'Blurred vision' in the eye ipsilateral to he pain	10	16	0	0	4	33
XIV.	Difficulty on swallowing	6	10	4	10	0	0

*$P<005$, two-sided Fisher's exact test comparing group A and B.
†See text.
‡It is possible that the external pressure exerted in our study has been too mild.

Table 3 Diagnosis in patients belonging to Groups A, B and C

	Group A ($n=62$)		Group B ($n=40$)		Group C ($n=12$)	
Diagnosis	*n*	%	*n*	%	*n*	%
CEH	34	55*	8	20	0	0
M	8	13	6	15	2	17
HN	0	0	10	25	0	0
CEH and M	10	16	0	0	2	17
CEH and HN	2	5	6	15	0	0
Non- classifiable	8	13	10	25	8	66

*$P<0001$, Fisher's exact test. CEH = cervicogenic headache; M = migraine without aura; HN = headache associated with neck disorders; CEH and M, CEH and HN = satisfied the diagnostic criteria of both headache categories. Non-classifiable = insufficient criteria for CEH, HN, M.

Patients diagnosed as CEH in Group A fulfilled 3.53 ± 0.51 criteria in addition to the inclusion ones, whereas M patients fulfilled far fewer criteria: 1.25 ± 0.46 ($P<0.001$, one-way ANOVA) (Table 4). In Group B, patients diagnosed as CEH fulfilled a significantly higher number (4.00 ± 0.00) of the diagnostic criteria (in addition to the inclusion one) when separately compared with M (1.67 ± 1.37) and with HN (2.60 ± 0.84)

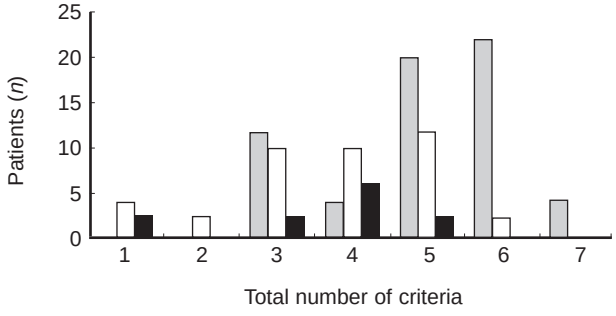

Figure 1 Frequency of the pooled diagnostic criteria (4) for CEH in Groups A, B and C.

Table 4 Mean number of diagnostic criteria for CEH (in addition to the inclusion criteria) in patients belonging to Groups A and B

Diagnosis	Group A (mean ± SD)	Group B (mean ± SD)
CEH	3.53 ± 0.51 (n = 34)*†	4.0 ± 0 (n = 8)*
M	1.25 ± 0.46 (n = 8)	1.67 ± 1.37 (n = 6)
HN	–	2.60 ± 0.84 (n = 10)

*CEH vs. M in Group A and B; CEH vs. HN in Group B: $P < 0001$, one-way ANOVA.
†CEH vs. the corresponding value in Group B: $P = 0006$, one-way ANOVA.

subjects. The Group C subjects could not be included in the statistical comparison as none of them presented a CEH diagnosis. Furthermore, the mean number of CEH criteria fulfilled in patients with a definite diagnosis of CEH (according to Table 1) was higher in Group A (3.53 ± 0.51, in addition to the two inclusion criteria) than in Group B (4.00 ± 0.00, in addition to the inclusion one) ($P = 0.006$, one-way ANOVA) (Table 4).

Sensitivity and specificity levels of the single diagnostic criteria in CEH patients are shown in Table 5 and Fig. 2. The temporal pattern (IV) and the moderate, non-pulsating headache (V) presented high sensitivity and specificity (≥75). Similarly, the shoulder–arm symptom criterion has a good specificity and acceptable sensitivity. It is worthy of note that the other symptoms and signs of neck involvement (excluding a reduced range of motion in the cervical spine) showed high specificity, but rather low sensitivity. Similarly, minor symptoms and signs presented very low sensitivity but high specificity. The anaesthetic blockade of the GON carried out in this study seems to be a specific but not a sensitive criterion.

Relationship with previous trauma

A head/neck trauma (whiplash type) had been sustained in 44 (71%) Group A patients, in 34 (85%) Group B patients and in 12 (100%) Group C patients; no statistically significant difference was found between the CEH patients of Group A and those of Group B as regards the number of previous traumas sustained (Table 6). In all cases, either the headache antedated the trauma or an interval of over 2 months (23.6 ± 27.3 months) had elapsed between trauma and headache onset. The interval between whiplash injury and headache onset was significantly shorter ($P < 0.005$; one-way ANOVA) in patients belonging to Group B (9.1 ± 8.8 months) than in those belonging to Group A (33.2 ± 30.3 months). In Group C patients, the interval between trauma and headache onset exceeded 6 months (26.4 ± 35.8). In eight cases the time of trauma could not be precisely documented.

Radiological findings

In our series, 49.1% patients had a normal X-ray of the neck. The presence of a spinal abnormality was significantly higher in Group B (30/40; 75%) than in Group A (16/62; 25.8%) ($P < 0.001$; Fisher's exact test) patients (Table 7). In Group C four of 12 (33.3%) had abnormal X-rays. In patients with radiological abnormalities (a requirement in the IHS classification), either a rectilinearization (X-rays) or disc protrusion/herniation (CT scan) was found. These findings were present with the same frequency on both the symptomatic and non-symptomatic sides (Table 7), indicating that an ordinary cervical spine X-ray is not really a sensitive enough method for a diagnosis of CEH. Cervical spine rectilinearization without disc herniation was the only finding in Group C. No significant distribution of the radiological abnormalities was found in patients within the diagnostic Groups A and B. Since Group C had only four cases of abnormal radiological findings, two of whom had the diagnosis of CEH + M, no statistical evaluation was carried out in this group. However, our findings have to be considered with caution because, due to ethical reason, a control material could not be collected.

Discussion

Headache related to the cervical spine is often misdiagnosed and treated inadequately because of confusing and varying terminology (17). Not all headache patients with relevant neck symptoms (i.e. signs and symptoms of neck involvement) can be properly classified using the IHS criteria. The original diagnostic criteria for CEH have been questioned, mainly due to the relatively limited number of patients described; even the very existence of this entity/syndrome has been

Table 5 Sensitivity and specificity of diagnostic criteria in patients fulfilling the CEH criteria

Diagnostic criteria		Group A	
		Specificity	Sensitivity
Major symptoms and signs			
I.	Unilateral headache	0	1*
II-a-1.	Pain triggered by neck movements and/or sustained awkward head positioning	0.75	0.44
II-a-2.	Pain elicited by external pressure over the GON or the ipsilateral upper, posterior neck region C2-C3	1	0.17
II-b.	Ipsilateral neck, shoulder and arm pain of a rather vague, non-radicular nature	0.88	0.65
II-c.	Reduced range of motion in the cervical spine	0.38	0.91
Pain characteristics			
IV.	Pain episodes of varying duration or fluctuating continuous pain	0.88	0.78
V.	Moderate, non-excruciating pain, usually of a non-throbbing nature	0.86	0.91
VI.	Pain starting in the neck, eventually spreading to oculo-fronto-temporal areas	0	1*
Other important criteria			
VII.	Anaesthetic blockades of the GON or C2 root	1.0	0.18
IX.	Sustained neck trauma a relatively short time prior to the onset	0.88	0.65
Minor, more rarely occurring, non-obligatory symptoms and signs			
Xa-b.	Rarely occurring nausea, vomiting, and XII photo- and phonophobia	0.88	0.48
Xc.	Ipsilateral oedema and, less frequently, flushing, mostly in the periocular area	0.88	0.09
XI.	Dizziness	0.75	0.26
XIII.	'Blurred vision' in the eye ipsilateral to the pain	1.0	0.22
XIV.	Difficulty on swallowing	0.88	0.09

* Inclusion criterion.

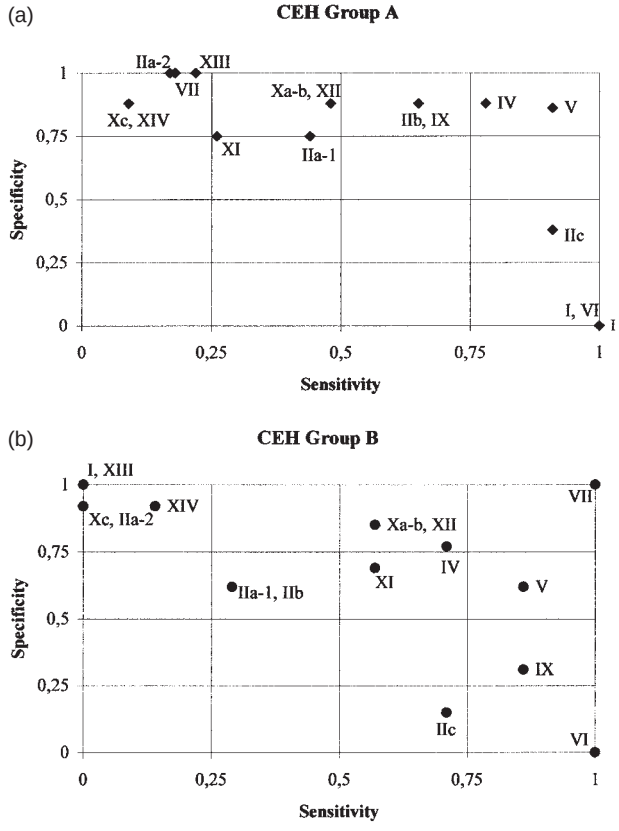

Figure 2 Sensitivity and specificity in patients fulfilling the CEH criteria (Group A upper panel, Group B lower panel).

questioned. In a recent review, Leone et al. (18) criticized various advances made in the field of CEH. The unfortunate conclusion reached by these authors, i.e. that of non-existence of CEH, we consider as unwarranted. This conclusion can largely be criticized due to the overt shortcoming of the study methodology (i.e. non-prospective studies) and to various misunderstandings (of the concepts of 'unilaterality of pain', of clinical examination of 'neck range of motion', etc.) (3, 19). The lack of objective information in this field is due to the relatively small number of prospective studies published.

The present study indicates that application of the two criteria used in the classification of our Group A represents a putative initial step that might allow the identification of 'possible' CEH patients; the application of a further three diagnostic criteria increases considerably the likelihood of correctly identifying 'probable' CEH cases. Therefore, the criterion of unilaterality, as described in the revised classification of CEH (20), may seem to be a crucial diagnostic piece of evidence. Unilaterality of pain as defined in the original criteria was probably too 'strict' a criterion, while the revised, somewhat 'loosened', definition seems in our experience to be more acceptable nosographically.

Applying the original CEH diagnostic criteria, we identified 42/114 (37%) patients with CEH; 16/114 (23%, respectively: 9% HN and 14% M) fulfilled the criteria for an IHS diagnosis of HN ($n=10$) and M ($n=16$), while the other 26 would be attributed the IHS diagnosis of 'headache not fulfilling the listed criteria' (migraine-like?). Moreover, there was, in our series, no overlapping of diagnostic criteria between M and HN. However, 20/114 (17%) patients satisfied the criteria for both CEH and M or for both CEH and HN (IHS). In these cases, it was hard to assess with precision during the clinical interview, whether these were concomitant or overlapping diagnoses.

CEH is steadily gaining credence as a diagnostic alternative, and the criteria currently applied do allow a clear distinction to be drawn between CEH and CPH, hemicrania continua and chronic daily headache (21). Nosographic difficulties apart, CEH is becoming increasingly accepted thanks to improvement of the therapeutic approach (22, 23).

Clinical evidence of neck involvement was present in the majority of our sample (60/114; 52.6%) and the percentage was even higher when considering those members of our population who fulfilled also the criterion of unilateral headache (42/62; 67.7%). The IHS classification criteria do not constitute an adequate basis for the proper nosographic evaluation of these patients.

Applying the original classification criteria of Sjaastad et al. (9), headache patients can be classified as cervicogenic on the basis of the presence of many characteristic diagnostic criteria.

However, as shown in the present paper, CEH still can overlap with migraine, on the one hand, and with

Table 6 Frequency of head/neck trauma (whiplash) in anamnesis

	Group A		Group B		Group C	
Diagnosis	*n*	%	*n*	%	*n*	%
CEH	28*/34†	82	8/8	100	–	–
M	6/8	75	4/6	67	2/12	17
HN	–	–	10/10	100	–	–
CEH + HN	2/2	100	6/6	100	–	–
CEH + M	6/10	60	–	2/12	17	–
Non-classifiable	2/8	25	6/10	60	8/12	67
Total	44/62	71	34/40	85	12/12	100

*Number of patients having sustained neck trauma.
†Total number of patients fulfilling the criteria for diagnosis.

Table 7 Frequency of cervical spine X-ray abnormalities in patients belonging to Groups A and B (due to the limited number of patients in group C, namely 12, these patients have not been inserted)

	No abnormalities				Rectilinearization				Disc herniation/protrusion			
	A		B		A		B		A		B	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
CEH	24/34	71	4/8	50	6/34	17	4/8	50	4/34	12	–	–
M	6/8	75	4/6	67	2/8	25	2/6	33	–	–	–	–
HN	–	–	–	–	–	–	4/10	40	–	–	6/10	60
CEH + HN	–	–	–	–	–	–	–	–	2/2	100	6/6	100
CEH + M	8/10	80	–	–	–	–	–	–	2/10	20	–	–
Non-classifiable	8/8	100	2/10	20	–	–	2/10	20	–	–	6/10	60
Total	46/62	74.2*	10/40	26.3	8/62	12.9*	12/40	30	8/62	12.9*	18/40	47.4

*Group A vs. Group B: $P<0001$, χ^2.

headache associated with disorders of the neck (IHS) on the other. Furthermore, using the current IHS diagnostic criteria for headache (24) there remain a relatively small number of patients that cannot be classified at all.

When seeking to distinguish M from CEH, 'migrainous' symptoms, like nausea and photophobia, represent a clinical challenge, especially when they are not marked. Moreover, in the migrainous population of Blau and MacGregor (25), two-thirds of their patients reported neck symptoms during attacks, and 43% recognized neck pain as a trigger factor for migraine attacks. However, findings from studies where one has failed to use a CEH category should be treated with caution.

Another diagnostic difficulty emerges when headache arising from the neck occurs simultaneously with M or TH. According to Pffaffenrath and Kaube (26), 56% of their patients had CEH in combination with other headaches. In the present study (Table 3) a coexistence of CEH with either M or HN has been found in 17% of the cases.

According to the original diagnostic criteria for CEH, a positive response to appropriate anaesthetic blockades of the GON, or of the facet joints, is essential for a positive diagnosis of CEH. In this study, we were unable to perform blockades in every case due to the pain severity. This diagnostic test could reduce the number of CEH cases associated with other headache forms and represent a diagnostic tool in the differential diagnosis of CEH vs. other unilateral headaches (27–29). In doubtful cases, patients should undergo diagnostic facet joint blocks, and, if necessary, provocative and analgesic discography, at appropriate levels, in an attempt to identify other sources of the pain (30).

No specific radiological abnormalities (by plain X-rays of the cervical spine) were identified in CEH by Pffaffenrath et al. (31) or by Fredriksen et al. (32), which underlines, at the present time, the fundamental importance of basing the diagnostic work-up of such patients on the clinical picture. Our data also support previous notions indicating that radiological abnormalities, when present, are probably not specific for CEH. It is admittedly a drawback that an age-matched control series could not, for ethical reasons, be obtained in the present study.

The frequency of headache with CEH characteristics 1 year after the traumatic event was 3% in the Oslo whiplash study (33). However, further prospective data are needed to clarify the role of whiplash in CEH. In our experience, CEH is not likely, in principle, to be a post-traumatic headache, since the frequency of head/neck trauma is not significantly higher in CEH subjects than in patients with other kinds of headache (i.e. M or HN). At least, it is unlikely to be the sole factor in most cases. However, it is not the percentage of traumas that counts, but the type of trauma in a given patient.

We feel that the number and the relative importance of the diagnostic criteria for CEH ('major criteria', 'pain characteristics', 'other important criteria') (9) constitute, at the present time, a relevant aspect in identifying patients. Our data indicate that at least five out of the seven 'pooled' criteria should be present in order to establish a diagnosis of CEH. Moreover, if pain first is experienced in the neck and then spreads to the fronto-ocular area and it is unilateral, the chance of correctly identifying patients as CEH instead of HN sufferers increases significantly (Table 3). Therefore, our findings confirm the importance of unilaterality and pain distribution as a mandatory requirement for CEH diagnosis.

In the type of patients selected with the two inclusion criteria employed in our study, temporal pattern and quality of the pain seem to be the two criteria showing the highest sensitivity and specificity. A similarly high specificity was found as regards symptoms and signs of neck involvement (in particular pain, of a rather vague, non-radicular nature, elicited by external pressure over the GON and ipsilateral discomfort in neck, shoulder or arm), the importance of which has been stressed in the revised classification criteria (20). This is partly in accordance with the view of Vincent (34), who also validated the sensitivity and specificity of the criteria for CEH, M and tension-type headache.

The revised diagnostic criteria for CEH developed by the Cervicogenic Headache International Study Group (20) probably constitute an important step forward, even though they need to be validated in large series of patients. Moreover, we already foresee the time when further areas of interest will be studied (personality factors, markers of neck movements, etc.) and experimental models will be available (effect of trauma, late whiplash syndrome) allowing CEH to be better characterized. However, our data should be considered with caution because the case selection could have an entrance bias, as the study was carried out in a headache centre population series of patients.

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Appendix 1. Cervicogenic headache: diagnostic criteria (9)

Major symptoms and signs

I. Unilaterality of the head, without sideshift.

II-a-1. Pain seemingly of a similar nature, triggered by neck movements and/or sustained awkward head positioning.

II-a-2. Pain, similar in distribution and character to the spontaneously occurring pain elicited by external pressure over the GON or the ipsilateral upper, posterior neck region C2-C3.

II-b. Ipsilateral neck, shoulder and arm pain of a rather vague, non-radicular nature.

II-c. Reduced range of motion in the cervical spine.

Pain characteristics

III. Non-clustering pain episodes.

IV. Pain episodes of varying duration or fluctuating continuous pain.
V. Moderate, non-excruciating pain, usually of a non-throbbing nature.
VI. Pain starting in the neck, eventually spreading to oculo-fronto-temporal areas, where the maximum pain is obtained.

Other important criteria
VII. Anaesthetic blockades of the GON or C2 root.
VIII. Female sex.
IX. Sustained neck trauma (whiplash) by history.

Minor, more rarely occurring, non-obligatory symptoms and signs
X. Nausea, vomiting, ipsilateral oedema and, less frequently, flushing, mostly in the periocular area.
XI. Dizziness.
XII. Photo and phonophobia.
XIII. 'Blurred vision' in the eye ipsilateral to the pain.
XIV. Difficulty on swallowing.

HEADACHE IN THE DIAGNOSIS-RELATED GROUPS (DRG) ERA: MANAGEMENT AND APPROPRIATENESS OF ADMISSION

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Headache is an extremely common disorder which has a marked impact on the utilisation of healthcare resources and constitutes a considerable socio-economic burden. The related costs, both direct and indirect, are especially high in developed countries, since headache predominantly affects an economically-active section of the population. The Diagnosis-Related Groups (DRG) system, a method for reimbursing healthcare structures for patient admissions, was introduced in Italy in 1995. The aim of the system was to control public health expenditure and to promote better distribution of financial resources. Here, we report the results of the application of the DRG system to headache patients admitted to the Department of Neurology of the University of Pavia in 1996 and 1998. The financial analysis revealed high fixed costs (hospital running costs per days of hospitalisation); by contrast, the impact of the variable costs (those relating to the direct management of the individual patient, i.e. examinations, therapeutic interventions etc.) was low. It was found that reducing the number of days of hospitalisation increases the hospital's income and reduces the mean loss incurred in each DRG.

It is therefore suggested that a complete approach to the management of headache must include educational programmes for patients and general practitioners, and that access to headache centres and to hospital care should be restricted to cases of acute, severe headache, or recurrent, chronic headache with/without drug abuse or dependence.

KEY WORDS: Appropriateness of admission, DRG, headache, management.

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INTRODUCTION

Headache is an extremely common disorder. About 90% of the general population suffers from "headache" during its lifetime. Migraine, in particular, afflicts up to about 18% of women and 6% of men. While not life-threatening, headache constitutes a socio-economic burden, and has a marked impact on the utilisation of healthcare resources. The socio-economic costs, both direct (examinations, drugs, procedures, days of hospitalisation) and indi-

rect (working days lost or reduced capacity to work) are very high in developed countries, since headache predominantly affects an economically-active section of the population. The considerable cost of managing headache penalises health services, national economic growth, the community and, last but not least, patients and their families. A recent study on a large population in the USA (1), reported that the cost of migraine to American employers (due to days off work and impaired working efficiency) amounts to about $13 billion a year. The annual direct medical costs for migraine care total approximately $1 billion, of which nearly $100 are spent per diagnosed patient; moreover, about 60% of the total burden is spent on outpatient visits (1).

Despite its high prevalence, headache has not been regarded in the past as a public health priority because it is not considered a serious illness.

In recent years, the Italian National Health Service (NHS) has introduced several innovations, one of which is the Diagnosis-Related Groups (DRG) system (2). As from 1995, the year in which the system was first implemented, the term DRG has become increasingly familiar in Italy. It refers to a method for the reimbursement of healthcare structures which depends strictly on diagnosis on discharge, and is based on the medical facilities provided by a hospital. The DRG system was introduced as a means of keeping public health expenditure under control and of improving the distribution of financial resources. The DRG system implies the need for an appropriate control of patient admission, which, in turn, is restricted to life-threatening diseases.

Procedures are surveyed by the Italian NHS according to the Protocollo di Revisione Utilizzo dell'Ospedale (PRUO), which is based on the Appropriateness Evaluation Protocol (AEP) adopted in USA. The aims of PRUO are: 1) to evaluate the appropriateness of admissions and to draw comparisons between hospitals and units; 2) to evaluate the appropriateness of hospital stays (is there a valid reason for the hospitalisation of patient "x" on day "y"?); 3) to evaluate the efficiency of case history archives; and 4) to evaluate and verify the correctness of principal diagnosis. Admissions and hospitalisations are governed, among other variables, by the following criteria: critical health conditions and the need for medical observation for at least 3 times per day.

We have previously reported the evaluation of one year's admissions (using the new DRG system) of "headache" sufferers to our neurological institute, paying particular attention to problems relating to the compilation of the patient discharge form (3). The present study analyses the application of the DRG system to "headache" patients at the C. Mondino Institute of Neurology in Pavia in the years 1996 and 1998. The study focuses on cost problems and assesses the appropriateness of admission and the management of headache patients.

METHODS

We considered the diagnoses on discharge for all types of primary headache in years 1996 (2nd year of implementation of the DRG) and 1998 (4th year); the first year of application (1995) was not considered due to the possible lack of homogeneity of the data.

The DRG numbers applicable to the various headache types and derived from the ICD-IX codes (4) are listed in Table I. Atypical facial pain is embraced by DRG 18 and 19; numbers 24 and 25 are applicable to migraine headache in adults, and 26 to migraine in children. Tension-type headache is included in DRG 243 or, more correctly, in 427. DRGs 435 and 437 refer to migraine or tension-type headache with drug abuse or dependence and detoxification/rehabilitation therapy. As well as examining the frequency of each DRG number

Table I - DRGs and ICD-IX codes mainly used for headache disorders

DRG	ICD-IX code	Definition of DRG
18	350.8	Cranial & peripheral nerve disorder with CC
19	350.8	Cranial & peripheral nerve disorder without CC
24	346.0 / .1 /.2 / .8 / .9, 784.0	Headache age > 17 with CC
25	346.0 / .1 /.2 / .8 / .9, 784.0	Headache age > 17 without CC
26	346.0 / .1 /.2 / .8 / .9, 784.0	Headache age 0-17
243	723.1	Medical back problems
427	307.8	Neuroses (except depressive)
435	304.8, 305.4 / .9	Drug abuse or dependence, detoxification or other symptomatic treatment without CC
437	304.6 / .8	Drug dependence, combined rehabilitation & detoxification therapy

Abbreviations: CC = complication and comorbidity

and the length of hospital stay, we also carried out an analysis of economic costs.

The fixed costs for the hospital stay (daily expenses per DRG per number of days) are related to the running of the hospital as a whole. Variable costs, meanwhile, are generated by the direct management of the individual patient, i.e., examinations, medical procedures, tests and therapeutic interventions. The sum of the fixed and variable costs produces the total cost to the hospital. The income generated in each DRG was calculated on the basis of the expenses incurred by the hospital and the relative reimbursement obtained from the NHS.

RESULTS

Table II shows the number of the diagnoses of "headache" with respect to the total diagnoses of neurological diseases. In 1998, our department also provided a Day Hospital (DH) service; a diagnosis of headache was made in 26.8% of DH patients.

Table III reports the frequency of each DRG. Headaches classifiable as DRG 437 increased from 4.5% in 1996 to 25.6% in 1998.

Table II - Diagnoses on discharge of headache patients (all types) from the C. Mondino Institute of Neurology in the years 1996 and 1998

	1996	1998
Total neurological diagnoses (no.)	4,791	4,159
Diagnoses of "headache" (no.)	602	536
% of total	12.6	12.9
Day Hospital		
Total diagnoses	n\a	875
Diagnoses of "headache"	n\a	235
% of total	n\a	26.8

Abbreviation: n\a = data not available

Table III - Frequency of headache DRGs (expressed as percentage values) in the years 1996 and 1998

DRG	1996	1998	D.H. (1998)
18	0.8	0.0	0.0
19	3.0	0.2	0.0
24	19.4	18.1	6.8
25	31.4	34.7	72.8
26	31.5	8.2	4.7
243	12.6	0.7	0.0
427	12.0	9.1	15.3
435	4.8	3.4	0.4
437	4.5	25.6	0.0

DRG 25 was the main diagnosis in DH patients (accounting for 72.8%), but its frequency in hospitalised patients was similar to that observed in 1996. Within DRG 25, migraine with aura accounted for 23.7%, while cluster headache, atypical migraine forms and non specific headaches accounted for 22.1%. The remaining 54.2% was represented by migraine without aura.

In 1998 the length of the average hospital stay decreased in almost all the DRGs, particularly in DRG 19 and 437 (Table IV).

With regard to costs, we found that fixed costs were higher than the variable ones in all cases (Fig. 1) in both years.

The hospital's mean income for each DRG is shown in Fig. 2. In 1996 losses were incurred in relation to 4 DRG (19, 25, 427, 435), whereas in 1998, losses were recorded only in relation to DRG 435.

The cost of headache to the Italian NHS with respect to our Institute was 2,277,934,000 Italian Lire (ITL) in 1996 and 2,895,932,000 ITL in 1998 (corresponding to a 27.1% increase). As in 1998 DH reimbursement amounted to 94,034,000 ITL, the increase in total cost to the NHS was of 31.3%.

Table IV – Mean length of hospital stay for the various DRGs

DRG	1996 (days)	1998 (days)
18	7.6	–
19	9.39	3.0
24	8.04	7.75
25	6.03	5.9
26	4.72	4.82
243	7.09	5.25
427	7.24	6.49
435	7.62	7.33
437	10.22	7.74

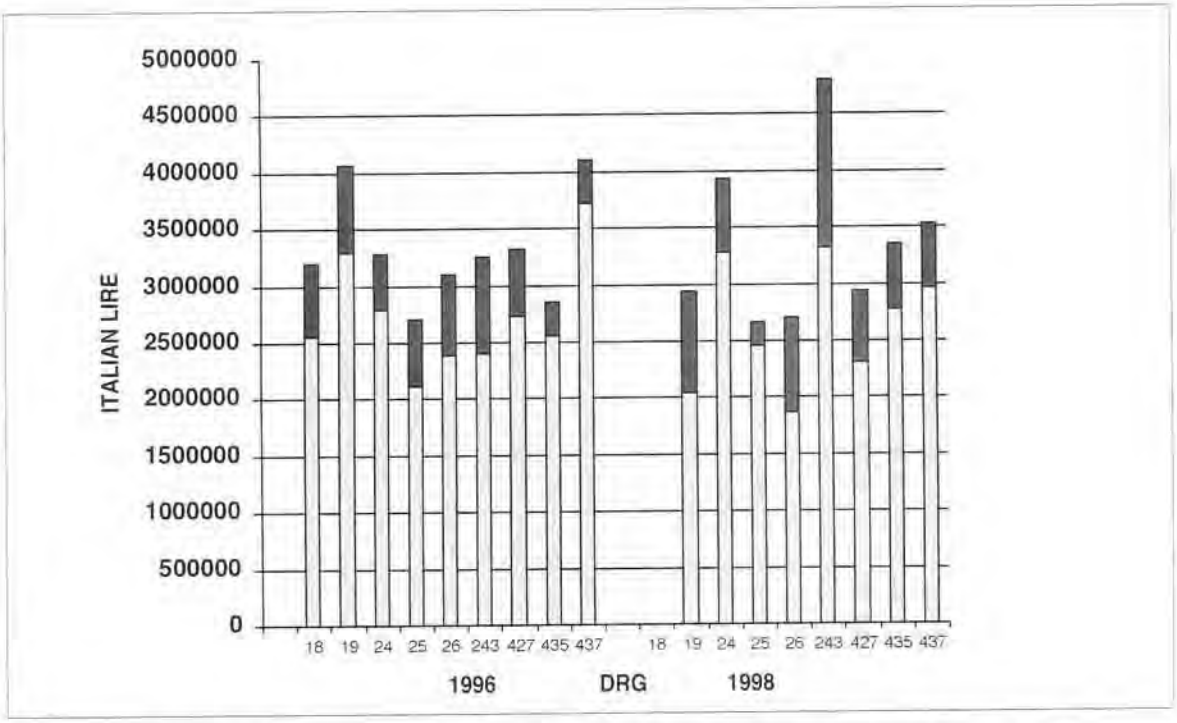

Fig. 1 - Average fixed and variable costs per DRG in 1996 and 1998; mean values are expressed in Italian lire. Grey bars = fixed costs, black bars = variable costs.

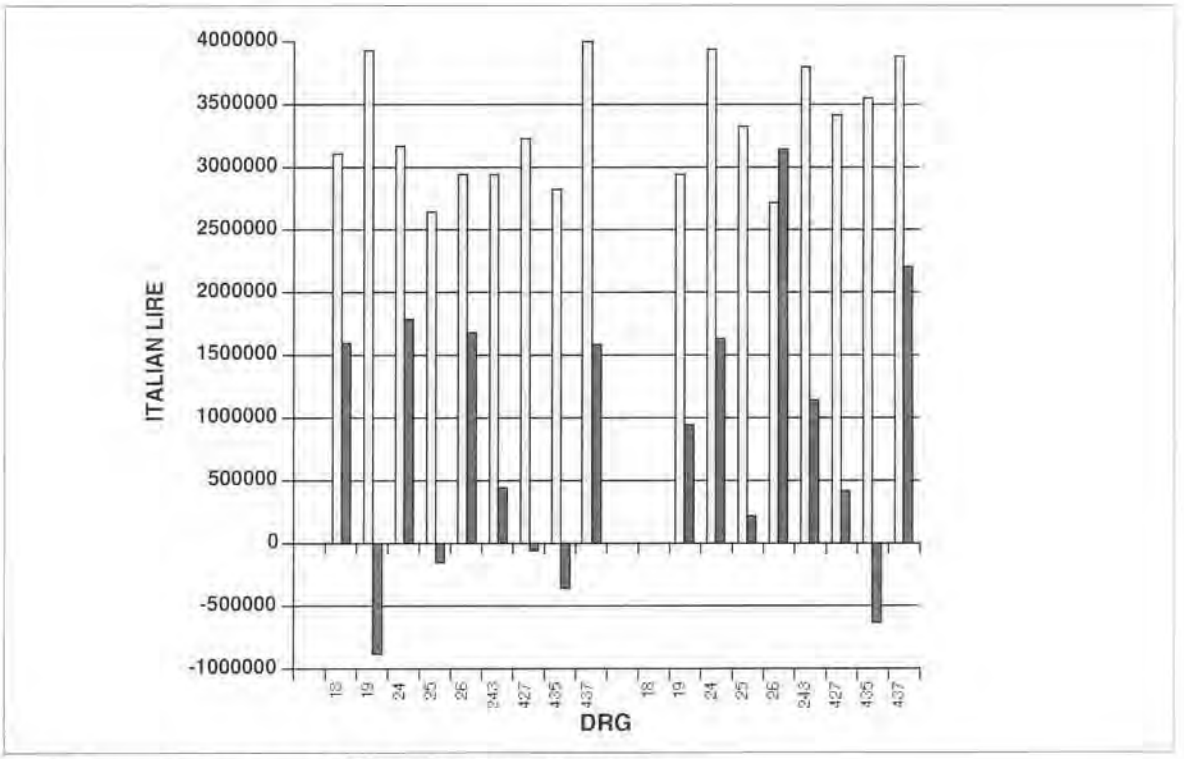

Fig. 2 - Average income for each DRG in 1996 (left) and 1998 (right)
Mean values are expressed in Italian lire: total costs = grey bars, income = black bars.

DISCUSSION

The percentage of diagnoses of headache was similar in the 2 years considered (12.6% vs 12.9%). Upon analysis of the frequency of the various DRGs in the two years, a strong increase emerged in 1998 in the number of admissions (for detoxification/rehabilitation therapy) of drug dependent headache sufferers: this is a positive trend as these are the patients who really require hospitalisation according to PRUO/AEP guidelines. Surprisingly, there was also a high number of diagnoses in DRG 25 (migraine without complications and comorbidity) in 1998 (34.7%), a group of patients who should, more correctly, be managed as outpatients or as DH patients. A possible explanation could be the presence, in this DRG, of migraine with aura (23.7%), a form of primary headache which sometimes gives rise, initially, to problems of differential diagnosis, as it presents similarities with transient ischemic attacks. In addition, the presence of cluster headache and other atypical forms of migraine (22.1%) contributed to the increase in this DRG.

In each DRG, the financial analysis revealed high fixed costs (general hospital running costs) generated by hospital stays, while the impact of the variable costs on the expenses incurred was low. It also revealed that reduction of the number of days of hospitalisation increased the hospital's income and reduced the mean loss in each DRG.

According to the NHS patient admission control procedure (PRUO/AEP system), admission for "headache" is justified only in cases characterised by: 1) the need for medical examination and observation due to the presence of a new and/or acute severe headache

(symptomatic headache?); 2) the need for detoxification/rehabilitation therapy (headache with drug abuse or dependence). Since all other admissions could count as "inappropriate", it suggested that the global management of headache patients should be based on the integrated use of outpatient and DH facilities, with admission restricted to a small number of specific cases.

In the light of the PRUO system, a number of our admissions were probably inappropriate as in the case of several patients in DRG 25 (migraine without complications and comorbidity), 243 and 427 (tension-type headache). It should also be noted that, due to the considerable cost of hospital stay, the admission of these patients contributes to the inflation of NHS charges. The present data, in light of the recommendations of the Task Force of the International Headache Society (5) on the organisation and delivery of services to headache patients, suggest that the global management of headaches should be structured on a number of levels or consecutive steps. These involve specialists, general practitioners and patients, as follows:

Level 1 - the provision of educational programmes for patients aimed at increasing their basic knowledge of different headache types, and at enabling them to identify precipitating factors and alarm signals (the need for emergency consultations);

Level 2 - the provision of ongoing medical education programmes for general practitioners, covering complete headache history, diagnosis of headache types and primary care in non complicated headaches;

Level 3 - the involvement of specialists and headache centres concentrating on cases which are difficult to diagnose (atypical or complicated forms), on headache with comorbidity (where there is a need for particular examinations or procedures), and on headache which is not responsive to the various treatments;

Level 4 - the admission to hospital, should finally be reserved for cases of sudden severe headache (e.g., of suspected secondary nature) and chronic headache with drug abuse or dependence.

While reflecting the present situation of the Italian health organisation, this is, in our opinion, a valid scheme for headache management and one that would be destined to favour the economic growth of the NHS. A link and continuous exchange between general practitioners and headache specialists must be considered the cornerstone of any drive to improve the employment of healthcare resources.

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Asymmetrical reduction of the nociceptive flexion reflex threshold in cluster headache

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The nociceptive flexion reflex (NFR) of the lower limbs (RIII reflex) was examined bilaterally in 54 cluster headache (CH) patients suffering from episodic CH (ECH) and chronic CH (CCH). Fifteen ECH patients were examined in both remission and active phases. The RIII reflex threshold (Tr) and the threshold of pain sensation (Tp) were significantly reduced on the symptomatic side in patients with episodic CH during the bout. During the active phase of episodic CH an inverse correlation was found between the severity of CH (ratio: number of cluster periods/years of illness duration) and the Tp, which may suggest a role for secondary central sensitization in pain pathways. The lower Tr and Tp on the symptomatic side is in keeping with previous observations exploring pain mechanisms using different methods (i.e. corneal reflex, pain pressure threshold). On the whole, these data tie in with the view of an impairment of the pain control system, which parallels the periodicity of the disorder in the episodic form. □ *Cluster headache, pain threshold, nociceptive flexion reflex, asymmetry*

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The pathogenesis of cluster headache (CH) is still far from clear. The temporal pattern of the attacks, the lateralization of the pain and the oculocephalic signs provide interesting aspects for exploration of the mechanisms involved. Both central and peripheral mechanisms have been suggested in order to explain the origin of the pain and the accompanying symptoms (1, 2); in particular, impairment of the trigeminal pain control system and/or trigemino-vascular system have been hypothesized in CH (3, 4), while recent data stress the pathogenetic role of hypothalamic pace-maker regions of the brain (5) which may play a permissive role, releasing or entraining the trigemino-vascular pain system.

Indirect instrumental and clinical evidence suggests central sensitization in the pain control system (at trigeminal level, in particular), lateralized to the affected side, which may be responsible for the allodynia (6) and hyperalgesia reported by some CH patients either on cephalic or extracephalic parts of the body, e.g. neck and shoulder ipsilaterally (7) or extended to the entire hemisoma (8).

An impairment of the pain transmission system outside the active period has been found and thus involvement of the central tonic pain mechanisms in the pathogenesis of CH has been suggested (9).

The present study aimed to explore, through the nociceptive flexion reflex (NFR) of the lower limbs (RIII reflex), the pain control system in CH patients in the active period and in remission. This neurophysiological method has been used in previous studies to investigate the mechanisms involved in the antinociceptive activities in several pain conditions, including primary headaches (10–14).

Moreover, since the hypothalamus is known to receive nociceptive afferents from the brainstem reticular system and to project heavily onto the periaqueductal grey (PAG) (15, 16), which exert inhibitory control on both the trigeminal and the spinal neurones involved in the transmission of nociceptive messages (17, 18), the NFR

could yield information about the activity of these structures in CH.

Materials and method

Study population

Fifty-four patients diagnosed as having CH according to the classification of the International Headache Society (IHS) (19) were recruited from among the people seeking treatment at the University Centre for Adaptive Disorders and Headache (University of Pavia, Italy). Thirty-six patients were suffering from episodic cluster headache (ECH) (31 males (M) and five females (F); mean age 38.0 ± 13.2 years; mean illness duration 9 ± 6 years). Twenty-three tests were carried out in the ECH patients during an active period (ECHp) (19 M and 4 F; mean age 36.7 ± 13.0 years) and 28 tests in patients during a remission phase (ECHr) (25 M and 3 F; mean age 37.2 ± 13.2 years). In 15 ECH patients the examination was repeated in both a cluster phase and a remission phase.

The patients were considered to be in an active period when severe attacks had been occurring more than once daily for at least 10 days. The patients were considered to be in a remission phase when no attacks had occurred for at least 2 months. Eighteen chronic cluster headache patients (CCH) (16 M and 2 F; mean age 44.3 ± 12.7 years; mean illness duration 10.5 ± 8.2 years; frequency of attacks: 1.3 ± 0.7/day) underwent the same investigation. According to the IHS classification nine were chronic form *ab initio* and 12 secondarily chronic. Twenty-one healthy individuals (19 M and 2 F; mean age 33.7 ± 5.2 years) served as a control group.

All patients and controls were right-handed. At the time of testing, the subjects had been drug-free for at least 24 h, except for O_2 inhalation. None of the patients had been treated with ergot-containing medications or with sumatriptan for a period of 2 weeks prior to the study. Prophylactic treatment was tapered off 6–32 weeks before testing. Two cases (ECH in active phase) received a single dose of steroids (desametasone 4 mg 1 fl i.m.) 7 and 10 days before the examination. In the active phase the patients were examined 6–18 h after the attack. All patients gave their informed consent before entering the study. The study was approved by the local ethics committee.

Experimental procedure

During the session, the subjects sat comfortably in an armchair, in order to achieve general muscle relaxation. The RIII reflex was elicited bilaterally (randomly first on the right or symptomatic side, then on the left or non-symptomatic side, or vice versa in each patient) according to a method described elsewhere (10, 14). The reproducibility of this method has been previously documented (20). Briefly, the sural nerve was stimulated with a pair of surface electrodes placed on degreased skin at the retromalleolar site. The stimulus consisted of a volley of 10 rectangular pulses (1 ms duration at 300 Hz), delivered by a constant current stimulator at random intervals (5–20 s). Muscular response was recorded electromyographically from the biceps femoris muscle (capitis brevis) using surface electrodes. The RIII reflex is a nociceptive reflex of the lower limb, that originates from stimulation of Aδ and C fibers, in particular. The minimal intensity of current needed to elicit a reflex response and its maintenance for 80–90% of the time of stimulation was taken as the reflex threshold (Tr). In addition, the threshold of the subjective pain sensation (Tp) was also noted, while recording the RIII reflex.

The Tp and Tr were determined using the staircase limits method following a standardized procedure (10). The Tp was determined as the minimal intensity of current needed to evoke a first perceived pain sensation (i.e. perceived by the patient as pain, and no longer as a tingling sensation). Both Tp and Tr are linear functions of the intensity of stimulation and high correlation coefficients have been shown in healthy subjects. The Tp/Tr ratio is, in fact, usually close to one in normal subjects (10, 14). The symptomatic and non-symptomatic sides were, respectively, compared with the left and right sides of the control subjects. The examination was carried out at the same time of day (10.00–12.00) in all subjects so as to avoid any influence related to circadian variation of the RIII reflex threshold (20).

Statistical evaluation of the results

The data are expressed as mean $\pm$ standard deviations. A one-way ANOVA and the post-hoc Scheffè method was used for between-group comparison of the parameters investigated. The paired *t*-test was used for test–retest and side-to-side comparisons. The parameters investigated on the symptomatic side of each patient were compared with the non-symptomatic side and the left with the right side of the control group; *P*-values lower than 0.05 were regarded as significant. The Spearman rank correlation coefficient was also computed.

Results

The mean age and duration of the disease of patients with CCH and ECH were not significantly different (one-way ANOVA; $P > 0.1$). The mean age of the controls

did not differ significantly (one-way ANOVA; $P>0.1$) from that of the patients.

When evaluating the side-to-side differences, the Tp and Tr values in ECHp and in CCH were significantly (paired *t*-test; $P<0.05$) reduced on the symptomatic as compared with the non-symptomatic side. No significant (paired *t*-test; $P>0.1$) side-to-side differences were found for ECHr and controls (Figs 1 & 2).

ECHp patients showed a significantly (one-way ANOVA; $P=0.04$) lower Tr on the symptomatic side than ECHr, CCH and controls (Fig. 1). The Tp was also significantly (one-way ANOVA; $P<0.005$) reduced in ECHp on the symptomatic side in comparison with ECHr, CCH and controls (Fig. 2). No significant (one-way ANOVA; $P>0.1$) differences were found for the Tr and Tp between the non-symptomatic side in patients and controls. No differences were found between either side in the control group.

When ECH patients ($n=15$) were tested both in the active period and in remission, the Tr on the symptomatic side was significantly (paired *t*-test; $P<0.05$) lower in the active period than in remission (Table 1). The Tp values were also significantly (paired *t*-test, $P<0.05$) lower in the active period than in remission.

The difference in Tp and Tr between CH patients suffering from headache on the left ($n=28$) and right ($n=26$) sides was not significant.

The Tp/Tr ratios are reported in Table 2. No significant difference was observed between the sides in ECH and CCH and in ECH between remission and the active phase, and when compared with controls.

The ratio of the number of cluster periods/duration of illness was used to obtain an overall clinical parameter on the severity of CH in the episodic form. A negative correlation was calculated between the above ratio and the Tp in ECHp ($r=-0.56$; $P<0.05$), while no linear correlation was found between the number of attacks per day in CCH and Tp values ($r=-0.29$ $P>0.1$).

Table 1 RIII reflex threshold (Tr) and subjective pain threshold (Tp) values in 15 episodic cluster headache (ECH) patients. The same subject has been evaluated both in the active period and in remission (mean values ± SD)

	Active period	Remission
Tp (mA) symptomatic side	8.00±1.61*	9.64±2.43
Tp (mA) non-symptomatic side	9.11±1.55	9.64±1.46
Tr (mA) symptomatic side	10.14±1.91*	11.68±3.27
Tr (mA) non-symptomatic side	10.82±2.28	11.07±1.36

* $P<0.05$ vs. the corresponding value in remission (Student's paired *t*-test).

Discussion

The typical lateralization of pain and autonomic signs in CH has prompted several studies seeking a pathogenic interpretation of this strictly unilateral headache. While in the past, the autonomic dysfunction was investigated in order to clarify the pathogenesis of CH (21), more recently the focus of attention has shifted to the role of the trigeminal pain control system (2, 3). A trigeminovascular connection and an ortho/antidromic conduction in the trigeminal fibers in particular (4) can account for both a peripheral and a central cause of headache. In

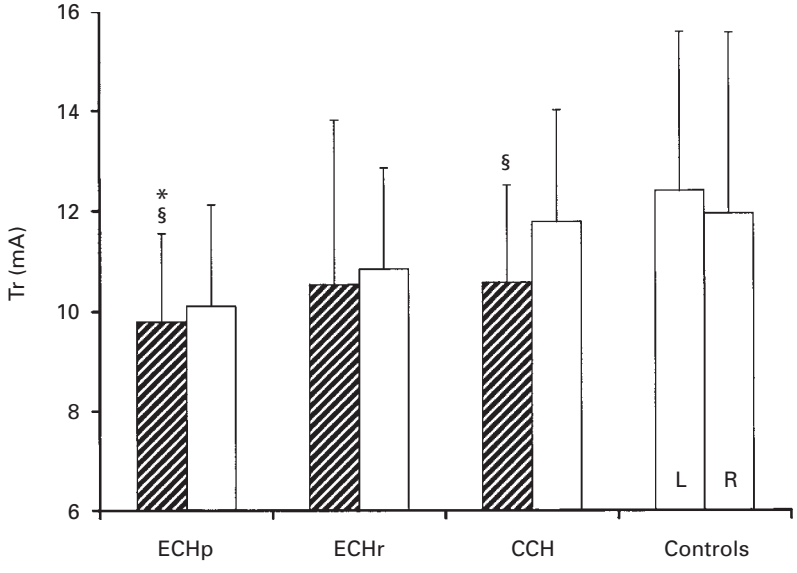

Figure 1 RIII reflex threshold (Tr) in episodic cluster headache in the active period (ECHp), in remission (ECHr), in chronic cluster headache (CCH) and in controls; (mean ± SD).* $P=0.04$ vs. controls (one-way ANOVA test). §$P<0.05$ side-to-side differences (paired *t*-test). L, left side; R, right side. Hatched columns = symptomatic side; open columns = non-symptomatic side.

Table 2 Tp/Tr ratio values in episodic cluster headache (ECH) patients in period and in remission, in chronic cluster headache (CCH) patients and controls. There are no significant differences between sides, groups and between period and remission phase

	Tp/Tr symptomatic	Tp/Tr non-symptomatic
ECH period	0.81±0.13	0.88±0.11
ECH remission	0.84±0.15	0.84±0.14
CCH	0.83±0.12	0.83±0.14
Controls	0.87±0.15(left)	0.87±0.13 (right)

a previous study, we documented a significant reduction of the corneal pain threshold (more evident on the pain side) in the active period, and a significantly reduced threshold of the nociceptive muscular response (corneal reflex) on the symptomatic side in CH during the active period (22).

These data suggest reduced inhibitory descending control on trigeminal nuclei in CH during the cluster period. More recent findings also suggest a hyperexcitability of the spinal trigeminal nucleus, as well as deficient descending inhibition by the hypoactive reticular nuclei, possibly related to hypothalamic disturbance and reduced central opioid activity (23). Involvement of the central tonic pain mechanisms in the pathogenesis of CH has also been suggested by a SPECT study during the cold water pressure test (9).

Since mid-brain and brainstem descending pain modulatory influences are common to trigeminal and spinal levels (18), it was of interest to study the threshold of the nociceptive flexion reflex (NFR) of the lower limbs in CH as indirect evidence of suprasegmental abnormalities. The RIII reflex in CH patients, both episodic, during active and remission phases, and chronic forms, were investigated in the present study.

NFR has proven to be an interesting neurophysiological tool for studying spinal and supraspinal pain processes in humans (11, 14).

A decrease in the RIII reflex threshold and the subjective pain threshold on the symptomatic side during the active phase in episodic CH compared with controls is the main result emerging from our investigation. Interestingly, during the remission phase the RIII reflex was within normal values, suggesting that a functional process underlies the pathogenesis of CH. Furthermore, the negative correlation between severity of disease and Tp values we found in ECHp suggests a predisposing condition to enhanced nociception and/or reflect central sensitization during the active period in those subjects who are more severely affected. These data agree with previous investigations concerning the instrumental exploration of autonomic responses to painful stimulation in this disease (25, 26). The data, suggesting that a region of the hypothalamus is activated only during the headache period (5, 27), may also explain why the RIII reflex was within normal values during the remission phase. However, an impairment of the pain transmission system outside the active period has also been reported (9).

Thyrotropin-releasing hormone (TRH) is known to produce changes in flexion reflex excitability (28), while

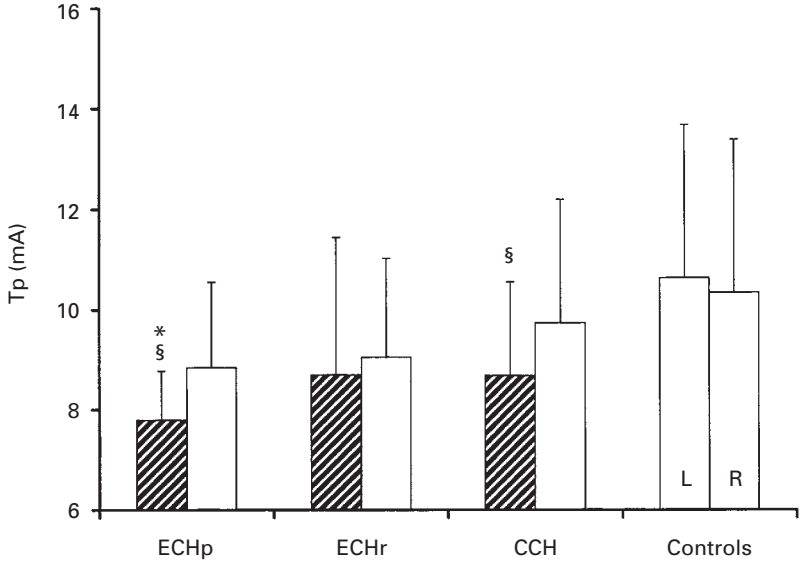

Figure 2 Subjective pain perception (Tp) in episodic cluster in the active period (ECHp), in remission (ECHr), in chronic cluster headache (CCH) and in controls; (mean ± SD).* $P<0.005$ vs. controls (one-way ANOVA test). §$P<0.05$ side-to-side differences (paired *t*-test). L, left side; R, right side. Hatched columns = symptomatic side; open columns = non-symptomatic side.

reduced response of prolactin to TRH has been found in female subjects in both phases of cluster headache and in chronic cluster headache (29). However, probably no relationship exists between the two phenomena, since a neuroendocrine influence should produce a bilateral effect in contrast with our results.

Since a decreased Tp/Tr ratio, as observed in tension-type headache, is considered related to a subjective amplification of pain perception (14), parallel changes in the Tr and the Tp observed in CH patients, indicate that psychological factors do not play a role in the pain perception changes observed in our subjects. An impairment in descending inhibitory controls could account for these concomitant changes in Tp and Tr values.

An asymmetry between the two sides is another important finding in our study. Abnormalities (increase in latency or reduction in amplitude) on the painful side have been described in CH patients during the active phase when studying the brainstem auditory evoked potentials (30) and visual evoked potentials (31), suggesting that a central mechanism is prominent in CH pathogenesis.

No difference between the left and the right side was observed in our subjects. These data are in agreement with the finding that the right-lateralized central processing observed in cluster headache patients during nitroglycerin-induced attacks was independent of the pain side (32).

The concept of a central mechanism (most probably dysfunction in the region of the hypothalamus) in CH pathogenesis is increasingly accepted, as a purely vasogenic cause cannot explain all the features of the disease (27). The circadian and circannual occurrence of the symptoms as well as altered hormonal/autonomic rhythms (33–37) may also indicate a centrally located dysfunction, even though haemodynamic mechanisms have also been suggested to explain these findings (2).

Recently, activation of the trigemino-vascular system in patients with acute spontaneous attacks has been postulated on the basis of the observation of an increase in level of calcitonin-gene related peptide (CGRP) and vasoactive intestinal peptide (VIP) in blood from the external jugular vein (38). Activation of a brainstem reflex, whose afferent arch is the trigeminal nerve, may account for these data (38). However, several central structures can be activated by the neural processing of craniovascular pain (39). Central neuroplasticity change or nociceptive sensitization might explain the phenomena, including hyperalgesia, which follow peripheral inflammation (40).

Even though the oculocephalic symptoms are the dominant feature of a CH attack, extracephalic pain can be observed in some patients, while cutaneous and deep hyperalgesia homolateral to the symptomatic side has also been described in CH patients (8, 36).

In the multiple comparison we failed to reveal significant abnormalities of Tr and Tp in chronic CH, even though we found a significant decrease on the pain side compared to the non-symptomatic side. Clinical heterogeneity (41) and the long-term use of prophylactic medications (i.e. lithium salts is known to interact with serotonergic and opiate receptors) (42), which may have induced changes in the sensitivity of receptors in the pain signalling system could explain the less evident alteration in chronic form.

In conclusion, our data confirm, by means of a neurophysiological method, the existence of a reduced pain threshold on the painful side also in extracephalic parts of the body in episodic CH patients during the active phase, indicating an involvement of the pain control system in this disorder.

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The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache

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Cephalalgia

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The administration of nitroderivatives in cluster headache (CH) sufferers is the most reproducible experimental paradigm to induce spontaneous-like pain attacks. Previous uncontrolled studies have reported that the local use of anaesthetic agents in the area of the sphenopalatine fossa is able to extinguish nitroglycerin (NTG)-induced pain in CH. The present study, carried out according to a double-blind placebo-controlled design, included 15 CH patients, six with episodic CH (mean $\pm$ SD age of 36.8 ± 5.6 years), and nine with chronic CH (37.8 ± 10.4 years). Patients had undergone a standard NTG test (0.9 mg sublingually), during which the intensity of pain was scored using a visuo-analogic scale (VAS, range 0–10). Nine patients (two with the episodic form, seven with the chronic form) experienced a typical, spontaneous-like attack on the usual side, occurring in all cases within 45 min. In these patients, the test was repeated with an interval of 2 days, and once pain intensity reached 5 on the VAS, a 10% solution of cocaine hydrochloride (1 ml, mean amount per application 40–50 mg), or 10% lidocaine (1 ml), or saline was applied using a cotton swab in the area corresponding to the sphenopalatine fossa, under anterior rhinoscopy. This was done in both the symptomatic and the non-symptomatic side, for 5 min. Treatments were always performed randomly, in separate sessions. All patients responded promptly to both anaesthetic agents, with complete cessation of induced pain occurring after 31.3 ± 13.1 min for cocaine and 37.0 ± 7.8 min for lidocaine ($M \pm SD$). In the case of saline application, pain severity increased thereafter, and extinction of the provoked attacks occurred with a latency of 59.3 ± 12.3 min ($P < 0.01$ and $P < 0.01$ vs. cocaine and lidocaine, respectively, Mann–Whitney *U*-test). While further suggesting that the sphenopalatine ganglion participates in the mechanisms of pain, these findings indicate that the local administration of the anaesthetic agents cocaine and lidocaine is effective on NTG-induced CH attacks, and may be used in the symptomatic treatment of this disorder. □ *Cluster headache, cocaine, nitroglycerin, lidocaine, pain, sphenopalatine ganglion*

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Introduction

Cluster headache (CH) is a type of primary headache characterized by a peculiar temporal pattern (circadian occurrence of pain attacks, and circannual onset of active phases), an almost constant localization of pain (reported as severe and of non-throbbing quality), and the presence of ipsilateral autonomic signs and symptoms involving oculo-cephalic functions (conjunctival hyperemia, lacrimation, ptosis, miosis, nasal stuffiness and/or rhinorrea) (1, 2). The diagnostic criteria of the International Headache Society (IHS), which are almost exclusively based on the clinical description and periodicity of symptoms, allow for the distinction of two main CH subtypes, namely an episodic form and a chronic form (3).

While the clinical features of CH are usually well-defined, uncertainty still exists as to the precise

pathophysiological mechanisms underlying the disorder. Autonomic dysfunction and cluster pain represent the aspects which have received most study, with considerable evidence suggesting that both phenomena may originate in the central nervous system (CNS). According to such a view, referred to as the 'central' hypothesis, CH patients may be characterized by derangement of the hypothalamic-limbic pathways subserving the autonomic, neuroendocrine and behavioural functions (1, 4, 5).

Various theories have been proposed to explain the generation of pain during CH attacks. An involvement of the sphenopalatine ganglion was originally suggested, following Sluder's first description of a syndrome closely resembling CH and referred to as 'sphenopalatine ganglion neuralgia' (6). According to these observations, the sphenoidal sinus has since been regarded as a region of considerable importance in the pathophysiology of CH, and several studies have been carried out on the treatment of this disorder by targeting the sphenopalatine ganglion and its afferent and efferent parasympathetic connections (7–11).

Several agents have been used in CH as a symptomatic approach, and inhaled 100% oxygen, ergotamine tartrate, and the more recently introduced 5-hydroxytryptamine(5-HT) receptor agonists, such as sumatriptan, appear to be effective in CH (12, 13). Despite this, in up to 15% of cases CH attacks remain refractory to any medication. The use of substances provided with local anaesthetic properties in CH has so far received little consideration (see 14 for review). Cocaine and lidocaine are two drugs widely used for their anaesthetic effects. Cocaine is provided with sympathomimetic activity via modulation of the uptake of noradrenaline in nerve endings, whereas lidocaine appears to exert its effects via conduction-blocking properties. Both drugs have been proposed as alternative agents in acute treatment of CH, by local intranasal administration, based on their effects on either spontaneous or provoked attacks in open studies (15–17).

These observations, in addition to their considerable clinical relevance, have further supported the view that the sphenopalatine ganglion may be importantly concerned in CH pathophysiology. However, in none of the studies mentioned above were the effects of both cocaine and lidocaine investigated in the same group of patients. Moreover, all the available data are derived from studies carried out according to uncontrolled experimental designs. We have therefore utilized the commonly adopted model of nitroglycerin (NTG)-induced headache (18) to test the effects of the intranasal application of lidocaine or cocaine or placebo in a group of CH patients. An additional aim of the present study was to obtain indirect information on the pathogenetic mechanisms of CH, and in particular to elucidate further whether the sphenopalatine region may be actively involved in the process of pain onset during CH attacks.

Methods

The selected study group consisted of 15 patients, 13 males and two females, presenting with headache at the Headache Centre of the Neurological Institute of the University of Pavia, and enrolled consecutively. All patients were suffering from CH in the active phase, according to the IHS criteria (3). Their mean $\pm$ SD age was 37.2 ± 7.8 years (range 29–56). Six patients suffered from episodic and nine patients from chronic CH. Of the chronic CH patients, four had a primary chronic form, and five a secondary chronic CH. The mean $\pm$ SD of symptom duration was 8.2 ± 4.7 years (range 3–17). All patients had appearances absolutely typical of CH, with a constant presence of autonomic accompanying signs and symptoms during their pain attacks. The mean duration of their usual pain attacks was 47.6 ± 13.7 min (range 20–75). This was calculated on the basis of at least five untreated attacks recorded by patients with a dedicated diary chart. The individual clinical features of the patients studied are reported in detail in Table 1.

At the time of testing, patients were having regular headaches, and none of them had taken any prophylactic medication for at least 1 week prior to the study. After obtaining formal approval from the local ethical committee and informed consent from all patients, a complete clinical history was collected. Then, a thorough othorhinolaryngological examination as well as an anterior rhinoscopy were preliminarly performed by an experienced othorhinolaryngologist, in order to rule out the presence of endonasal diseases or malformations. Otorhinolaryngological supervision was also provided during all test procedures.

Patients then underwent a standard headache-induction test, carried out by administering NTG (trinitrine) 0.9 mg sublingually in headache-free conditions. This dose, currently used at our department, has been found to induce typical pain attacks in about 70% of CH patients in active phase, a percentage similar to that reported by Ekbom with 1 mg NTG (18). Those patients experiencing a typical attack following NTG administration underwent the test in two further sessions. An interval of at least 2 days was allowed between the three study sessions. During each test, patients were resting in bed in a supine position, and their cardiopressor parameters (heart rate, arterial blood pressure) were continuously recorded using a vital signs monitor (Dynamap, Kriticon, Florida, USA).

The time of onset of pain, the possible occurrence of general autonomic symptoms, and any changes in the

Table 1 Clinical features of patients; ci = conjunctival injection; nc = nasal congestion; l = lacrimation; p = ptosis; r = rhinorrhea. Attack duration refers to the usual duration prior to the study

n	Age (yr)	Gender	Pain side	CH type	Symptom duration (yr)	Attack duration (min)	Autonomic symptoms
1	36	M	L	Secondary chr.	14	60	ci, nc, l, r
2	56	M	R	Secondary chr.	15	60	ci, nc, r
3	31	M	R	Primary chr.	5	35	ci, nc, l, p, r
4	53	M	L	Primary chr.	4	60	ci, nc, l, r
5	34	M	L	Secondary chr.	7	45	ci, nc, l, r
6	35	M	R	Episodic	13	40	ci, nc, l, p, r
7	41	M	R	Episodic	10	50	ci, l
8	31	M	L	Secondary chr.	3	40	ci, nc, l, p, r
9	29	M	R	Secondary chr.	4	75	ci, nc. l, r
10	42	M	R	Episodic	7	50	ci, nc, l, r
11	36	M	R	Episodic	10	45	nc, p, l, r
12	31	F	L	Episodic	1	20	ci, nc, l, r
13	33	F	R	Episodic	8	40	ci, l, r
14	36	M	R	Primary chr.	6	35	ci, nc, l, r
15	35	M	L	Primary chr.	17	60	ci, nc, l, r

degree of conjunctival injection, width of the palpebral fissure, pupillar diameter and nasal congestion (if present) were also recorded using a dedicated chart. Patients were asked to score the intensity of any provoked headache by means of a visuo-analogic scale ranging from 0 to 10 (0 = no pain, 10 = unbearable pain).

In all cases, once a spontaneous-like headache attack became established (pain intensity of at least 5 on the scale, usually 5–10 min after the very onset of pain), patients were asked to extend their head 45 degrees. A cotton swab previously immersed in a 10% solution of cocaine hydrochloride (1 ml, mean amount of application 40–50 mg), or 10% lidocaine (1 ml), or saline was then introduced into the nostrils, placed in the region corresponding to the sphenopalatine fossa of both sides, and left there for at least 5 min. We chose to administer the drugs on both sides since in the previous studies treatments used ipsilaterally to the symptoms had failed in relieving pain in a variable proportion of patients. Procedures were made according to a double-blind design; all nine patients received randomly the three treatments and completed the study. The time elapsed until obtaining pain relief, and the magnitude of headache and autonomic symptoms were assessed and reported in the chart. The pain extinction time was recorded for all treatments; patients were defined as responders when a decrease of 50% or over in pain intensity was observed after treatments.

The administration of local anaesthetics was never repeated, even in the case of incomplete relief after several minutes. However, for ethical reasons, patients were free to ask for a rescue treatment (sumatriptan 6 mg s.c.) whenever required. At the end of each test, patients were also instructed to contact the Headache Centre the following day, to report on the status of their headache.

Statistical analysis was made using the non-parametric Wilcoxon ranks test to compare to baseline the VAS values at different times after treatments. The Mann–Whitney *U*-test was used to compare pain intensity at different times between treatments, as well as the pain extinction times of different treatments. Differences were considered significant if $P < 0.05$. Data are expressed as mean $\pm$ SD.

Results

During the first session of the study, an overall number of 15 induction tests were performed. As shown in

Table 2 Clinical features of the nine NTG-responsive patients during induction test. See Table 1 for abbreviations

n	(yr)	Sex	CH type	Latency of induced pain (min)	Side of induced pain	Symptoms
1	36	M	Secondary chr.	21	L	ci, nc, l, r
2	56	M	Secondary chr.	19	R	ci, nc, r
3	31	M	Primary chr.	35	R	ci, nc, l, p, r
5	34	M	Secondary chr.	30	L	ci, nc, l, r
6	35	M	Episodic	25	R	ci, nc, l, p, r
8	31	M	Secondary chr.	41	L	ci, nc, l, r
11	36	M	Episodic	20	R	nc, l, p, r
14	36	M	Primary chr.	27	R	ci, nc, l, r
15	35	M	Primary chr.	40	L	ci, nc, l, r

Table 2, nine patients (two with the episodic form, seven with the chronic form) experienced a typical, spontaneous-like attack on the usual side, occurring in all cases within 45 min (mean ± SD of latency 28.6±8.4 min, range 19–41). Pain duration was similar to that of the usual attacks (range 38–60 min). Type and intensity of autonomic signs and symptoms were also similar to those of the spontaneous attacks. In these nine patients, the NTG test was repeated with the previous use of anaesthetics, as described above.

As shown in Fig. 1, all patients responded promptly to both anaesthetic agents, as pain intensity decreased within the first 2 min and reached 3.5 for cocaine and 4 for lidocaine after 5 min (both $P<0.01$ vs. respective baseline values). In the case of saline, pain intensity further increased after intranasal application ($P<0.01$ vs. baseline, $P<0.001$ vs. both drugs). There was no significant difference between cocaine and lidocaine at all times, although a trend towards a better effect of cocaine was observed after 5 min ($P=0.07$ vs. lidocaine). Complete cessation of pain (Fig. 2) occurred after 31.3±13.1 min for cocaine, 37.0±7.8 min for lidocaine, and 59.3±12.3 min for saline ($P<0.01$ saline vs. both drugs). The duration of pain in the case of saline treatment was not significantly different from that of the usual, spontaneous attacks. Fig. 3 shows the number of pain-free patients and number of 'responders' at different times. After 10 min, there was no pain-free patient with any treatment, while responders were 3/9 for cocaine, 1/9 for lidocaine and 0/9 for saline; after 35 min all patients were pain-free with either cocaine or lidocaine, while all were still experiencing pain with saline.

None of the patients asked for rescue treatment, even though pain intensity was as high as 9 in one case treated with saline. Following the administration of both anaesthetics, a decrease was also observed in the intensity of autonomic signs and symptoms, which paralleled the reduction in pain severity (data not shown). Nasal congestion was attenuated more slowly, and complete resolution was obtained 5–10 min later than the other complaints. However, congestion of turbinates was mild in all patients, and in no case was the use of intranasal adrenergic decongestionants required to facilitate the access of solutions. Two patients found unpleasant the taste of the substance later identified as lidocaine, but the administration of both lidocaine and cocaine was generally well tolerated, and did not result in any significant side-effects. None of the patients experienced a spontaneous CH attack during the 5 h following lidocaine and 6 h following cocaine administration.

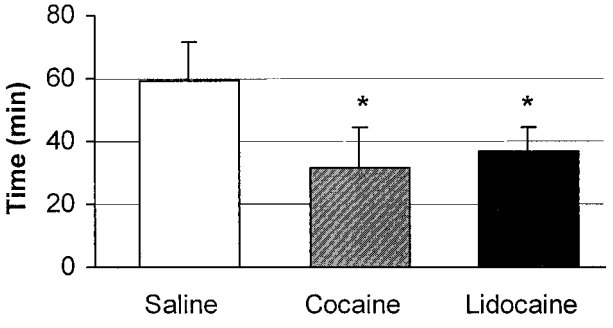

Fig. 2 Mean ± SD of pain extinction times following treatments in nine CH patients. * $P<0.01$ vs. saline.

Discussion

The application of cocaine to the area corresponding to the sphenopalatine fossa has been shown to be effective

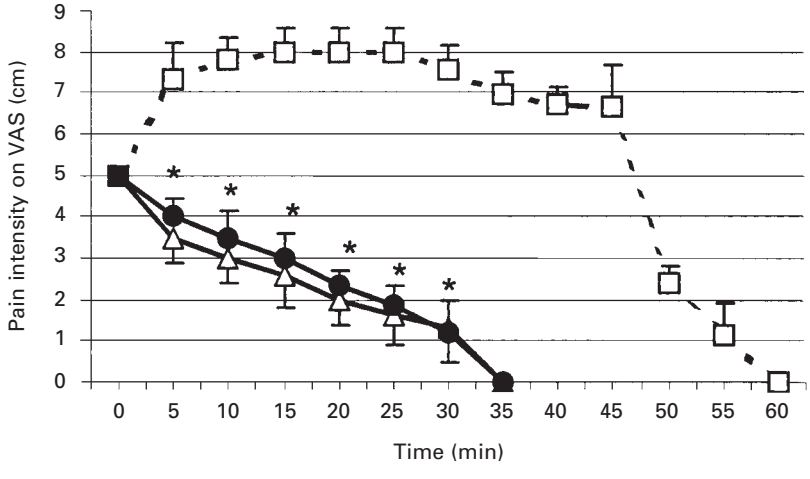

Fig. 1 Mean ± SD values of intensity of NTG-induced pain (visuo-analogic scale, VAS) in nine CH patients treated with intranasal cocaine, lidocaine or saline. * $P<0.001$, both drugs vs. saline, Mann–Whitney *U*-test. □= saline; ● = cocaine; △ = lidocaine.

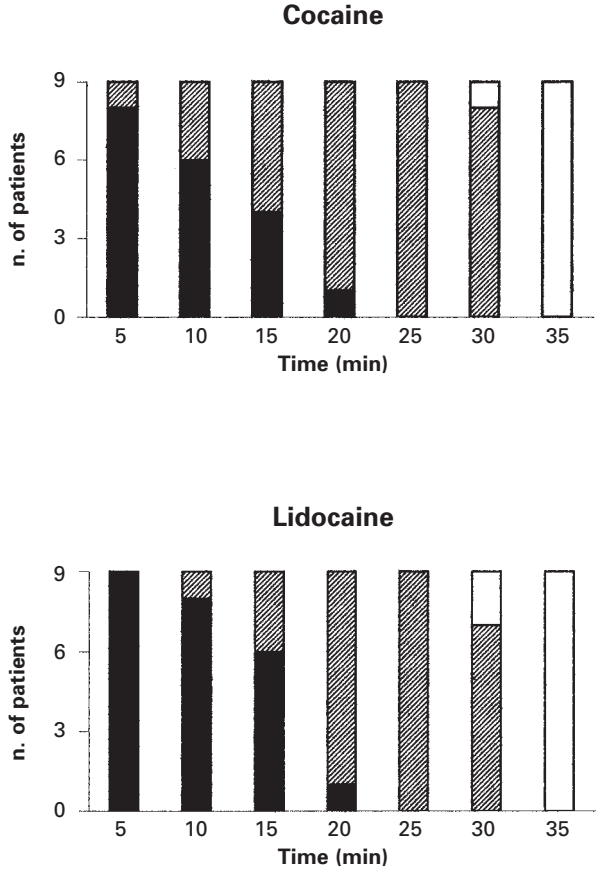

Fig. 3 Number of pain-free patients and responders at different times following treatments. □ = pain-free; ▨ = responders; ■ pain.

at extinguishing pain attacks in patients suffering from sphenopalatine neuralgia or other poorly defined related disorders (6, 7), which were likely to be CH forms. Other authors have also reported successful pain treatment in patients suffering from episodic or chronic CH using intranasal lidocaine during spontaneous attacks (16, 17). It is well established that spontaneous-like CH attacks can be triggered in predisposed individuals by the sublingual administration of NTG (18), which still represents the most reliable and reproducible paradigm of induced headache of the vascular type in humans. Also in migraine sufferers, the sublingual (19) or systemic (20) administration of NTG is indeed able to precipitate headache attacks, whose features resemble those of the spontaneous episodes and fulfil the IHS criteria for migraine. In addition to its effect on spontaneous attacks, intranasal lidocaine has been reported to be useful in relieving NTG-induced pain in CH patients (16). The effectiveness of locally applied cocaine under the same experimental paradigm has also been observed (15).

It is currently accepted that NTG acts via the production of the potent vasodilating mediator nitric oxide (NO) at the vascular level (21). Over the last few years, it has been proposed that patients with vascular headaches may display excess NO production and/or increased reactivity to the activation of the nitrinergic pathways (22). While the intimate nature of these processes remains unclear, it has been proposed that NO may be involved with a crucial role in the mechanisms leading to pain generation in both CH and migraine; in addition to its effect at the endothelial level, NO may also act centrally (brainstem nuclei), thereby participating in the processes underlying the onset of neurovegetative signs and symptoms in migraine and CH (23). Similar to CH patients, NTG-induced attacks in migraine sufferers have been recently shown to be significantly relieved by the intranasal application of lidocaine (24), further suggesting that these headache disorders may share common pathogenetic mechanisms.

The present study confirms, in a double-blind, placebo-controlled design, the previous observations that cocaine and lidocaine acting in the sphenopalatine region are both effective at reducing pain intensity in CH attacks (15–17). Compared to the previous studies, the effect of anaesthetic drugs was found in 100% of our patients. Whether this depends on the fact that in our study lidocaine and cocaine were administered bilaterally is not known. The issue of CH pain laterality affecting the clinical response to anaesthetic administration has been previously addressed by Kudrow et al. (24). In all of our nine NTG-responsive patients, appearance of symptoms within or between cluster periods concerned consistently one side. In a previous study, the variable pattern of pain side resulted in the total failure of the bilateral alcohol infiltration of the sphenopalatine ganglion (8). A similar unsuccessful treatment with lidocaine was reported in the case of bilateral migraine (24). On the basis of our findings, it would therefore appear that the bilateral nasal administration of lidocaine and cocaine in CH patients would prove effective regardless of pain localization. Also in cases of strictly consistent pain side within and/or between clusters, anaesthetization of parasympathetic fibers of both ganglia may be beneficial.

Another possible explanation for the rate of pain relief found in our patients may be related to the procedure of drug administration used in our study, which involved anterior rhinoscopy. In the case of the administration of drugs by drop instillation, or using spray preparation, drugs may indeed face restricted access to the most critical region of the nasal mucosa (i.e. that corresponding to the sphenopalatine area), due to nasal obstruction, an accompanying phenomenon which is known to occur frequently in CH (2). At the same time, the different

means of drug administration (cotton swab as opposed to nasal dropper or spray) may also account for the fact that while the latencies of cocaine and lidocaine-induced attenuation of pain in our patients was prompt and similar to that previously reported (15–17), complete pain disappearance occurred considerably later.

The possible mechanisms of action of lidocaine and cocaine in easing CH pain are a matter of current debate. A reduction of afferent nociceptive inputs to the spinal trigeminal nucleus, as well as the block of nerve terminals of the glossopharyngeal nerve have been proposed (17). However, the hypothesis which has received most consideration is that both anaesthetic agents may act at the level of the sphenopalatine ganglion (16), which is thought to be importantly involved in pain generation (7–11). In particular, at variance with lidocaine (which is devoid of sympathomimetic activity), cocaine exerts systemic noradrenergic effects, which may account for the slightly more rapid effect compared to lidocaine observed in this study.

Cocaine has definite vasoconstrictive properties (25), and at least 50% of its peak plasma levels persist for approximately 3 h after intranasal administration (26). This may also account for the prophylactic-like effect reported by our patients after cocaine application (pain-free interval of at least 6 h), similar to that previously reported by Ekbom (18). However, both the findings of previous studies (15, 16) and the present observations suggest that its therapeutic effects may be mainly due to its anaesthetic activity. In this respect, it is of interest that the analgesic effect of cocaine has been recently found to involve activation of endogenous opioid peptide activity in the brain, whereas the activation of NO pathways (such as that following NO precursors) results in inhibition of the opioid system (27).

Our findings are also in agreement with the recently reported effectiveness of the sphenopalatine ganglion blockade in CH patients using radio-frequency lesioning (28). Recent experimental evidence further supports the role of the sphenopalatine ganglion in the pathogenesis of CH. Stimulation of ganglionic parasympathetic fibres has been found to result in vasodilation of pial vessels both in the animal and in the human (29). Moreover, it has been demonstrated that in rats the large cerebral vessels are surrounded by nerve fibres originating in the sphenopalatine ganglion; these fibres contain the NO-producing enzyme NO-synthase (NOS), and are known to mediate vasodilatory phenomena (30, 31).

In conclusion, while further suggesting that the sphenopalatine ganglion participates in the mechanisms of pain, our findings indicate that local anaesthetic agents are effective on induced CH attacks. The greater effectiveness of both cocaine and lidocaine seen in the present study compared to previous reports may pertain to the bilateral mode of nasal administration, as well as to increased access to the sphenopalatine area allowed by the use of rhinoscopy. While the present findings need to be confirmed in spontaneous CH attacks, lidocaine and cocaine may be considered as useful alternatives to conventional drugs in the symptomatic treatment of this disorder. In addition, intranasal delivery of headache medications is presently receiving increased attention (14), as it offers considerable advantages, due to the rapid onset of action, comfortable self-administration, and the possibility for the drug to be absorbed in spite of symptoms (nausea, vomiting) which limit or preclude oral intake.

Bearing in mind the risks of cocaine addiction (which are further increased in a highly disabling disorder like CH) (32), the established relationship between cocaine abuse and the development/worsening of vascular headaches (33, 34), and the relatively poor availability of the drug, the use of lidocaine appears to be by far preferable. However, in view of the absence of major acute side-effects, the administration of cocaine, if restricted to particular cases (i.e. only patients with episodic forms of CH, and refractory to all of the current symptomatic treatments), may also be useful.

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