



Diagnostic and therapeutic trajectory of cluster headache patients in Flanders

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Abstract

Objective : A fraction of cluster headache (CH) patients face diagnostic delay, misdiagnosis, undertreatment and mismanagement. Specific data for Flanders are warranted.

Methods : Data on CH characteristics, diagnostic process and treatment history were gathered using a self-administered questionnaire with 90 items in CH patients that presented to 4 neurology outpatient clinics.

Results : Data for 85 patients (77 men) with a mean age of 44 years (range 23-69) were analysed. 79% suffered from episodic CH and 21% from chronic CH. A mean diagnostic delay of 44 months was reported. 31% of patients had to wait more than 4 years for the CH diagnosis. 52% of patients consulted at least 3 physicians prior to CH diagnosis. Most common misdiagnoses were migraine (45%), sinusitis (23%), tooth/jaw problems (23%), tension-type headache (16%) and trigeminal neuralgia (16%). A significant percentage of patients had never received access to injectable sumatriptan (26%) or oxygen (31%). Most prescribed preventative drugs after the CH diagnosis were verapamil (82%), lithium (35%), methysergide (31%) and topiramate (22%). Despite the CH diagnosis, ineffective preventatives were still used in some, including propranolol (12%), amitriptyline (9%) and carbamazepine (12%). 31% of patients had undergone invasive therapy prior to CH diagnosis, including dental procedures (21%) and sinus surgery (10%).

Conclusion : Despite the obvious methodological limitations of this study, the need for better medical education on CH is evident to optimize CH management in Flanders.

Key words : Cluster headache ; mismanagement ; diagnostic delay ; undertreatment ; misdiagnosis ; Flanders.

Introduction

Cluster headache (CH) is the most severe primary headache disorder and has hence been nicknamed 'suicide headache' in the 1950's. Despite its rela-

tively low prevalence, estimated at about 0.1% of the population, CH should be easily recognisable because of its stereotypical presentation (May, 2005 ; Fischera *et al.*, 2008). The International Classification of Headache Disorders second edition (ICHD-II) criteria define a cluster headache attack as a (very) severe unilateral (supra-)orbital and/or temporal pain lasting 15 to 180 minutes (Headache Classification Committee of The International Headache Society, 2004). The pain should be accompanied by at least one of the following signs : ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, eyelid oedema, forehead and facial sweating, miosis, ptosis, or a sense of restlessness or agitation. The attack frequency is usually one to two per day, and the ICHD-II criteria suggest a frequency range from one every other day to eight per day. Eighty-five to 90% of the patients suffer from episodic cluster headache (ECH), with clusters of attacks separated by pain-free periods of at least one month per year. Ten to 15% of CH patients have attacks occurring for more than 1 year without remission or with remissions lasting less than 1 month, and suffer from chronic cluster headache (CCH) by definition. Although not embedded in the ICHD-II criteria, cluster headache attacks often display a striking circadian and circannual periodicity.

Effective treatments are available to manage cluster headache, and guidelines are available for both abortive (or acute) and preventive treatment (May *et al.*, 2006). Because of the rapid onset of excruciating pain, the acute therapy must be fast-acting. Normobaric oxygen, delivered via a non-rebreathing facial mask, at 12 l/min for 15 minutes provides rapid and effective relief (Cohen *et al.*, 2008). Sumatriptan 6 mg subcutaneously, up to twice daily, is another first-choice option for acute therapy (The Sumatriptan Cluster Headache Study Group, 1991). Intranasal sumatriptan 20 mg or zolmitriptan 5 to 10 mg nasal spray are useful alternatives to injectable sumatriptan

(van Vliet *et al.*, 2003 ; Cittadini *et al.*, 2006 ; Rapoport *et al.*, 2007). Preventive therapy can be subdivided into transitional (or short term) and maintenance prophylaxis. Oral or rectal ergotamine is generally too slow to provide timely relief for acute attacks, but can be used in the short term prevention of CH attacks that occur predictably during the day or night (Matharu and Goadsby, 2002). Corticosteroids are very effective and provide the fastest action of all preventatives (Couch and Ziegler, 1978). Long-term side effects limit the use of steroids, but they are an appealing option during the time needed for the long-term maintenance therapy to take effect (Dodick, 2005). Suboccipital injection of corticosteroids and lidocaine is an effective short term treatment with evidence from placebo-controlled studies (Ambrosini *et al.*, 2005 ; Afridi *et al.*, 2006). The mainstay of maintenance prophylaxis for both ECH and CCH is verapamil (May *et al.*, 2006). The starting dose is 240 mg/day, but dose escalation up to 960 mg/day may be necessary. Electrocardiographic monitoring is indicated (Cohen *et al.*, 2007). Methysergide, lithium and topiramate are alternative preventive treatment options (May *et al.*, 2006).

Despite the well-described diagnostic criteria, many cluster headache patients face diagnostic delay and misdiagnosis (Klapper *et al.*, 2000 ; van Vliet *et al.*, 2003 ; Bahra and Goadsby, 2004). Effective treatment options are available, but undertreatment and mismanagement are not uncommon (Klapper *et al.*, 2000 ; Bahra *et al.*, 2002). Medication-overuse headache may further complicate CH (Paemeleire *et al.*, 2006). With this study we wanted to study the diagnostic and therapeutic trajectory of cluster headache patients in Flanders and identify problems of diagnostic delay, misdiagnosis, mismanagement and undertreatment (Van Alboom *et al.*, 2008).

Patients and methods

Five Flemish neurologists with a special interest in headache invited consecutive cluster headache patients that presented to neurology outpatient clinics to participate in this study by filling in a questionnaire with 90 items about their clinical features, as well as diagnostic and therapeutic trajectory. The Ethics Committees of the 4 participating hospitals approved the study (EC project number 2006/479) and all patients signed an informed consent form.

The data for all numerical, dichotomous and categorical variables were assembled in a database, which was analysed with Statistical Package for the Social Sciences (SPSS). Only patients with cluster headache according to the ICHD-II criteria were

included in the final analysis. The results were statistically evaluated as needed using bivariate correlation (Spearman correlation coefficient), Mann-Whitney U test, Kruskal-Wallis test and Chi-squared test. The significance level was set at $\alpha = 0,05$.

Results

STUDY GROUP

Ninety-five of 126 contacted patients filled in the questionnaire, yielding a response rate of 75%. Ten patients did not strictly meet the ICDH-II criteria and were therefore excluded from the analysis. Eight of them reported mean attack duration of more than 180 minutes. One of these 8, together with another patient, experienced more than 8 cluster attacks per day. A last one denied accompanying autonomic symptoms or restlessness. Among the 85 patients with cluster headache according to the ICHD-II criteria, were 77 men and 8 women (male-to female ratio of 9.6) with a mean age of 44 years (range 23-69). The mean age at onset was 32 years, with a standard deviation (SD) of 12 years. The youngest age at onset was 14 years, the oldest 60 years.

CLINICAL FEATURES

All 85 patients in the study presented with a typical and recognisable form of cluster headache. ECH was recorded in 79% and 21% suffered from CCH. The ECH group experienced an average of 2 cluster periods per year, lasting 1-4 months in 71%. During a cluster period, half of the patients had a frequency of 1-3 attacks per day, with mean attack duration of 1-3 hours in 54%. Eighty-three percent of patients described the pain as 'excruciating', no one as 'mild' or 'moderate'. Fifty-one percent reported a history of suicidal ideation due to the pain intensity but no one ever attempted to commit suicide. The pain was mostly strictly unilateral, but switched from side to side in 16 patients (19%), either between 2 cluster periods or between attacks of the same cluster period. In line with the ICHD-II criteria, the pain was mainly felt at the retro-orbital (61%), temporal (58%) or peri-orbital (54%) region or on the forehead (54%). However, the pain was experienced over a wide area by many patients, including upper teeth and upper jaw in 48% as well as neck, vertex, nose and occiput in more than one fifth (Fig. 1). Autonomic symptoms were present in all but one person. Ninety-four percent had a feeling of restlessness and 85% felt a strong tendency to move about. Additional accompanying symptoms were

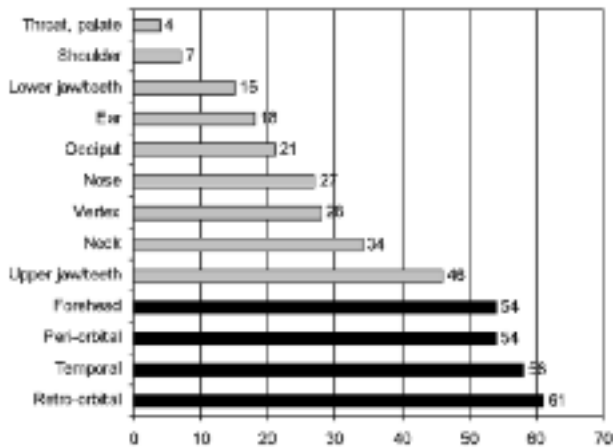


FIG. 1. — Distribution of pain location (in percentage). Black bars indicate site of pain corresponding with ICHD-II criteria.

also common, including photophobia (60%), phonophobia (53%), nausea (24%) and vomiting (19%) during a cluster attack. Fifty percent of patients reported at least one visual symptom (including blurred vision, zig-zag line, flashes, scotoma) before or during the headache attack, and also sensory (9%) or speech/language (16%) disturbances were reported, but the data were insufficient to allow aura diagnosis.

DIAGNOSTIC DELAY

The mean time between the first cluster headache attack and the first consultation of a physician (referred to as patient's delay) was 11 months (SD 25, median 2, minimum 0.1, maximum 120 months). After the first consultation an average of 35 months (referred to as physician's delay) were necessary to make the CH diagnosis (SD 72, median 5, minimum 0, maximum 468 months). The mean total delay (sum of patient's delay and physician's delay) between the first attack and the diagnosis of CH is 44 months (SD 75, median 12, minimum 0.5, maximum 480 months). Figure 2 shows that 54% of patients are diagnosed within a year after onset of cluster headache. For the remaining 46% of patients however more than a year elapsed before CH diagnosis and for 31% even more than 4 years. Statistical analysis revealed some factors associated with significant increase in both physician's delay and total delay, including a lower age at onset and pain that does not reach its peak within the first 5 minutes. On the contrary, a higher number of accompanying autonomic symptoms is associated with significantly shorter patient's and physician's delay. The presence of photophobia, phonophobia or nausea, an episodic

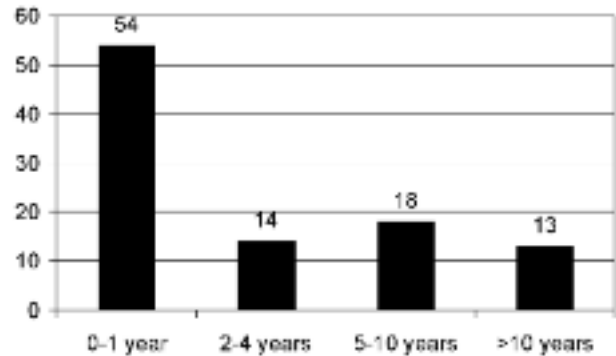


FIG. 2. — Distribution of total delay (in percentage) between first cluster headache attack and cluster headache diagnosis.

CH pattern, or pain alternating sides were not significantly associated with increased diagnostic delay. Fifty-two percent of patients visited at least 3 physicians prior to CH diagnosis (Table 1). Six percent of patients needed more than 6 different physicians and 18% more than 10 physician visits before a CH diagnosis was made. The first consulted physician in the majority of cases (77%) was a general practitioner, who also diagnosed CH in 11% of patients. However, CH is most frequently (80% of all cases) diagnosed by neurologists. Four percent of patients made a diagnosis of CH themselves. Besides neurologists, a variety of specialists were consulted, including at least one Ear, Nose, and Throat (ENT) specialist (30%), dentist (29%) and ophthalmologist (27%).

MISDIAGNOSIS

Cluster headache was the initial diagnosis in only 16% of patients (Table 2, left half). Sixty-five patients reported the misdiagnoses that were made during the diagnostic process (Table 2, right half), including migraine in about half (5 patients indeed suffered from both migraine and cluster headache), and sinusitis or dental pathology in about a quarter each. Also tension-type headache and trigeminal neuralgia were frequently diagnosed in about one in six patients each. The headaches were attributed to ophthalmological problems (including myopia, presbyopia and retinal disease) in 10%, to neck or back problems (including osteoarthritis and slipped disc) in 7%, and to nose problems (including septal deviation and vasomotor rhinitis) in 5%. Statistical analysis showed lack of association between misdiagnosis of migraine and the presence of phono-

Table 1

Distribution (in percentage) of number of physicians consulted by patients prior to cluster headache diagnosis (Physician number), type of first consulted physician (First physician) as well as type of physician who eventually makes the cluster headache diagnosis (Diagnosis by...)

Physician number	% patients	First physician	% patients	Diagnosis by...	% patients
0	9	GP	77	Neurologist	80
1	20	Neurologist	13	GP	11
2	19	Dentist	6	Self-diagnosis	4
3-6	46	Ophthalmologist	3	ENT specialist	1
7-10	6	ENT specialist	1	Ophthalmologist	1
				Anesthesiologist	1
				Dentist	0

ENT = ear, nose, and throat ; GP = general practitioner.

Table 2

Distribution (in percentage) of patients as a function of number of wrong diagnoses (Diagnoses number), and as a function of specific misdiagnoses (Misdiagnosis)

Diagnoses number	% patients	Misdiagnosis	% patients
0	16	Migraine	45
1	42	Sinusitis	23
2	16	Tooth/jaw problem	23
3-6	23	Tension-type headache	16
7-10	3	Trigeminal neuralgia	16
		Ocular problem	10
		Neck/back problem	7
		Nasal problem	5

or photophobia, nausea or vomiting, premonitory symptoms, or a family history of migraine. There was no significant correlation between misdiagnosis of sinusitis and pain location, seasonal variation, rhinorrhoea or nasal congestion. The diagnosis of a dental problem was not made significantly more in patients with pain radiating to the teeth or jaw. The diagnosis of tension-type headache was not associated with certain pain locations or with stress as subjective headache trigger.

MISMANAGEMENT

Prior to the diagnosis of cluster headache, 79% used non-specific analgesics, mostly paracetamol and nonsteroidal antiinflammatory drugs, but also salicylates and narcotic analgetics. Of the 67 patients that answered the question, 31% underwent some type of invasive therapy. 21% underwent a dental procedure (including tooth extraction and dental denervation) and 10% sinus surgery. Other treatments, each reported by one person, are nasal septoplasty, injections of homeopathical treatment in the temple and cervical disc surgery. Five patients were prescribed spectacles, 2 patients were sent to a physio-

therapist, one person underwent regularly nose washouts and one patient underwent light therapy. Also after the CH diagnosis was made, inappropriate therapies were prescribed, including carbamazepine (12%), propranolol (12%) and amitriptyline (9%). Four patients underwent repetitive intranasal administration of Bonain solution (mixture of cocaine, menthol and phenol) as prophylaxis. Alternative therapies were tried by at least 40 patients, in descending order acupuncture (22 patients), osteopathy (15 patients), and chiropractics (13 patients), homeopathy (11 patients), herbal therapy (9 patients), spiritual healing (6 patients), reflexology (5 patients) and hypnosis (2 patients).

UNDERTREATMENT

Subcutaneous sumatriptan and oxygen are the most prescribed abortive treatments, but a significant proportion of patients never had access (26 and 31% respectively). Moreover patients were most satisfied with these treatments as 93% and 75% of patients experiencing adequate pain relief with injectable sumatriptan and oxygen respectively. In 81% of patients oxygen was administered via a non-

Table 3
Percentage of patients having ever used specific acute and preventive therapies

	All CH patients (% ; n = 85)	ECH (% ; n = 67)	CCH (% ; n = 18)	P-value
ACUTE THERAPY	96	97	94	0,520
Sumatriptan SC	74	73	78	0,770
Oxygen	69	67	78	0,566
Triptan tablet/suppository	45	47	39	0,602
Sumatriptan nasal spray	16	16	17	1
Lidocaine nasal spray	8	8	11	0,642
Zolmitriptan nasal spray	5	6	0	0,572
PREVENTIVE THERAPY	90	89	94	0,680
<i>Transitional prophylaxis</i>				
Corticosteroids	54	52	61	0,598
Ergotamine	31	32	28	1
<i>Maintenance prophylaxis</i>				
Verapamil	82	80	89	0,503
Lithium	35	24	72	< 0,001
Methysergide	31	25	56	0,020
Topiramate	22	16	44	0,021

ECH = episodic cluster headache ; CCH = chronic cluster headache ; SC = subcutaneous.

rebreathing mask, but 19% used a nasal cannula or had used it in the past. The duration of the oxygen administration was at least 15 minutes in 65% of the 45 patients who answered the question. Forty-three patients also reported the flow rate, which was sufficient (at least 7 l/min) in 96%. Of the 40 patients with known method of administration, duration and flow rate, only 63% received oxygen in a fully correct way. The other abortive treatments were rated effective in less than 50%. Forty-five percent of patients had used triptan per rectum of orally. Verapamil (82%) and oral corticosteroids (54%) are the most prescribed preventive therapies. Patients were most satisfied with verapamil (82%) and oral corticosteroids (81%), followed by lithium (55%) and methysergide (52%). Only 15% of patients were satisfied with topiramate prevention. The duration of the corticosteroid therapy is known in 27 cases, and was less than 20 days in 5 patients, one month in 11 patients, and between 2 months and 2 years in 11 patients. CCH patients use lithium, methysergide and topiramate significantly more than episodic patients ($p < 0.05$). In 1 of the 15 people with known duration of methysergide therapy, it exceeded the limit of 6 months without at least 1 month drug holiday.

Discussion

Diagnostic delay and suboptimal treatment have been reported in both clinic-based and population-

based CH patient series in three separate studies in the United States, The Netherlands and the United Kingdom, using an internet survey, questionnaire or direct interview (Klapper *et al.*, 2000 ; van Vliet *et al.*, 2003 ; Bahra and Goadsby, 2004). The present study demonstrates that at least a fraction of cluster headache patients in Flanders face similar problems, despite typical CH characteristics fulfilling ICHD-II criteria and despite published guidelines on cluster headache treatment. A number of patients have been excluded from the study, mainly because their attack duration exceeded 3 hours which, however, is not an uncommon finding (Klapper *et al.*, 2000 ; van Vliet *et al.*, 2006). The remaining patients have typical cluster headache features, although some also report well-known additional clinical features, such as photophobia, phonophobia, nausea, extratrigeminal pain, and side-shift of attacks (Bahra *et al.*, 2002). Patients with CCH are overrepresented (21%), but this is not unexpected in an outpatient clinic-based series because of the difficulties with managing this condition (Bahra *et al.*, 2002 ; Bahra and Goadsby, 2004). An unexpected finding however is that women are underrepresented in this series as the usual male-to-female ratio in recent studies is rather 2 to 3 in stead of 9.6 in our study (Manzoni, 1998 ; Klapper *et al.*, 2000 ; Bahra *et al.*, 2002 ; van Vliet *et al.*, 2003 ; Bahra and Goadsby, 2004). This finding suggests underrecognition of CH in women in Flanders. Indeed, the decreasing preponderance in men in other studies (Manzoni, 1997 ; Manzoni,

1998) is most likely due to increased recognition rather than a true increase in prevalence in women (Bahra and Goadsby, 2004). Aura symptoms have been reported in a significant proportion of cluster patients (Bahra *et al.*, 2002) but can not be reliably detected with this questionnaire. The use of a visual aura rating scale in questionnaires remains to be validated (Eriksen *et al.*, 2005).

The mean age at onset of CH was 32 in our series, which is similar to previous studies (Manzoni, 1998 ; Klapper *et al.*, 2000 ; van Vliet *et al.*, 2003 ; Bahra and Goadsby, 2004). On average, the CH diagnosis was delayed by more than 3.5 years from the onset of symptoms and only half of the patients had a cluster headache diagnosis within the first year. About 25% of diagnostic delay is due to patient's delay. The main reason for this delay may be the natural evolution of ECH : once the cluster period is over patients see no reason to visit a physician. Additionally gender differences may play a role as headache consultation rates were shown to be smaller in men (Latinovic *et al.*, 2006). The average delay between first medical consultation and diagnosis of cluster headache is almost 3 years, which is in line with previous observations (Klapper *et al.*, 2000 ; van Vliet *et al.*, 2003 ; Bahra and Goadsby, 2004) but lower than an internet-based survey in the USA (Klapper *et al.*, 2000). The median physician's delay is however significantly lower at only 5 months, which indicates a subgroup of patients with a disproportionate longer delay in diagnosis. About half of the patients consulted at least three health care professionals, often including a dentist, ophthalmologist or ENT specialist, who rarely make the diagnosis. Previous studies indicated a CH sufferer typically sees 3 to 4 physicians prior to diagnosis (Klapper *et al.*, 2000 ; Bahra and Goadsby, 2004), and about one third of patients see a dentist and ENT specialist (van Vliet *et al.*, 2003). Further analysis of the data provided little explanation for longer physician's delay, except for lower age at onset and slow onset of pain. Early age of onset was associated with increased physician's delay in a previous study (van Vliet *et al.*, 2003). On the contrary, pronounced autonomic symptoms with CH attacks were associated with significant shorter physician's delay. Our data do not confirm an earlier observation that the presence of photophobia, phonophobia or nausea, episodic CH pattern or pain alternating sides (19% of patients in our series) are partly responsible for diagnostic delay (van Vliet *et al.*, 2003). Indeed these symptoms could be seen as part of the cluster headache spectrum (Bahra *et al.*, 2002).

The CH diagnosis is most often made by a neurologist. A key to improving diagnosis of CH

however is at the level of the general practitioner, who is the first consulted physician in more than 75% but makes the diagnosis in only 11% of patients. The Flemish neurologist diagnoses 80% of all cases, which is more than the 50% reported in the United Kingdom (Bahra and Goadsby, 2004). In our series 4% of CH patients self diagnosed, but this amounted to 13 to 16% in previous studies (van Vliet *et al.*, 2003 ; Bahra and Goadsby, 2004). Only 16% of patients were immediately diagnosed with CH, in the other patients misdiagnoses of migraine (in 45%), sinusitis (in 25%) and dental problems (in 25%) are most frequently made. These 3 most frequent misdiagnoses are the same in a Dutch study (van Vliet *et al.*, 2003). The mean number of misdiagnoses was 3.9 in the United States (Klapper *et al.*, 2000). Our data suggest misdiagnosis is due to insufficient knowledge of the CH criteria, rather than overlapping symptoms with other disorders.

One third of the patients in this study underwent invasive therapy, mostly involving the teeth or sinuses. These procedures are potentially harmful and can be avoided by early CH diagnosis. Previous studies showed that 16% of patients underwent tooth extraction, and 5-12% an ENT operation (Klapper *et al.*, 2000 ; van Vliet *et al.*, 2003). Forty percent of patients seen by another health care professional than a neurologist underwent an invasive procedure in the United Kingdom (Bahra and Goadsby, 2004). Alternative or complementary medicine is frequently explored by patients but has no scientific basis in CH (Bahra and Goadsby, 2004 ; Rossi *et al.*, 2008). After cluster headache was diagnosed, inappropriate medication was still prescribed to some, including carbamazepine, propranolol and amitriptyline in more than 10% of patients. Effective abortive treatments are underused, as 25% of patients never had access to subcutaneous sumatriptan and 30% never tried oxygen. Despite lack of evidence for efficacy 45% of CH patients used expensive triptans peroral or per rectum. Among those who did have oxygen prescribed, administration was frequently incorrect using a nasal cannula. The majority of patients get access to preventive treatment for CH according to current guidelines although there is an issue of prolonged use of corticosteroids, apparent underuse of verapamil, and, only in 1 patient in our study, prolonged use of methysergide with risk of systemic fibrosis. Underuse of effective abortive and preventive treatments as well as use of unproven treatments has been previously reported (Klapper *et al.*, 2000 ; Bahra and Goadsby, 2004).

There are some obvious methodological limitations to this study. A selection bias of more severe cases due to the clinic-based setting is certainly

present and is illustrated by the enrichment of CCH patients in our series. However, a population-based study on the subject is impractical and has only been realised once through an internet survey (Klapper *et al.*, 2000). In this internet survey an average diagnostic delay of 6.6 years and an average number of (Klapper *et al.*, 2000). A second potential issue is that of recall bias, which is inherent in a retrospective design, whether it is using a questionnaire, Internet survey or interview (Klapper *et al.*, 2000 ; van Vliet *et al.*, 2003 ; Bahra and Goadsby, 2004). Finally, initial diagnosis of CH by neurologists may be over-represented.

Cluster headache is rather rare with an estimated prevalence of 0.1% of the population. However, one has to recall the excruciating character of the pain in CH, driving half of the patients to suicidal thoughts at some point and having significant impact on social functioning, quality of life and use of healthcare resources (Jensen *et al.*, 2007). Early recognition of CH will prevent unnecessary suffering, and prevent medical shopping as well as potentially harmful invasive treatments. There is a need to ameliorate education on CH criteria and therapeutic guidelines. The primary target group should consist of general practitioners and medical students (Bahra and Goadsby, 2004), but also other health care providers, including dentists, ophthalmologists and ENT specialists, should be addressed. Despite considerable progress to be made, it is reassuring that diagnostic delay has significantly decreased over the decades (Bahra and Goadsby, 2004).

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