EXPERT REVIEWS

Misdiagnosis of hemicrania continua

Expert Rev. Neurother. 9(9), 1371–1378 (2009)

Mario FP Peres†, Marcelo M Valença and André Leite Gonçalves

†*Author for correspondence*
Al Joaquim Eugenio de Lima, 881 cj 708, 01403-01001 Sao Paulo, Brazil
Tel.: +55 113 285 5726
Fax: +55 113 285 5726
marioperes@yahoo.com; http://cefaleias.com.br/enxaqueca

Hemicrania continua (HC) is a primary headache disorder that is characterized by a continuous unilateral headache of moderate severity, exacerbations of severe pain, and complete responsiveness to indomethacin. Misdiagnosis of HC is probably common in general neurology settings and other clinical specialties. This paper is an attempt to bridge the gap between the correct and misdiagnosis of this disorder. HC was once thought to be a rare headache disorder, but is, in fact, an underecognized headache syndrome. HC can be of continuous or remitting form. Variants such as HC with aura have been described and secondary cases may occur. Indomethacin is the best treatment, although HC could respond to other NSAIDs, such as the selective COX-2 inhibitors.

Keywords: diagnosis • hemicrania continua • migraine • primary headaches

Hemicrania continua (HC) is one of the primary chronic daily headache (CDH) disorders. It is an indomethacin-responsive headache disorder characterized by a continuous, moderate-to-severe, unilateral headache that varies in intensity, waxing-and-waning without disappearing completely, with exacerbations of severe pain, and associated migrainous and autonomic features (tearing, nasal congestion, conjunctival injection, ptosis, rhinorrhea and eyelid edema). HC almost invariably has a prompt and enduring response to indomethacin.

Exacerbations of severe pain are often associated with autonomic disturbances (ptosis, miosis, tearing, conjunctival injection and sweating). Migrainous features (photophobia, phonophobia and nausea) may also occur. HC is not triggered by neck movements but tender spots in the neck may be present.

Previously, HC was thought to be a rare disorder. However, Peres *et al.* reported the largest case series (34 patients) so far showing HC is more common than previously believed [1].

Almost invariably HC has a prompt and enduring response to indomethacin. However, the requirement of a therapeutic response is problematic since it excludes the diagnosis of HC in patients who were never tried on or who failed to respond to indomethacin. Silberstein *et al.* proposed a slightly modified diagnostic criteria for HC [2] and the second edition of the International Classification for Headache Disorders now includes HC diagnostic criteria (Box 1). Pareja *et al.* mention different points proposing how the dilemma of response to indomethacin could be solved [3].

Hemicrania continua takes precedence over the diagnosis of other types of CDH. CDH refers to the broad group of people with very frequent headache (15 or more days per month; duration greater than 4 h). The major CDH subtypes are chronic (transformed) migraine (CM), HC, chronic tension-type headache (CTTH), and new daily persistent headache (NDPH) [2].

History & early descriptions

The earliest recognition of a headache syndrome involving one side of the head is attributed to Aretaeus of Cappadocia (second century AD). However, Egyptian descriptions appear in papyri dating from 1500 BC [4]. Galen (131–201 AD) introduced the term 'hemicrania' for unilateral headache. It was later transformed into the old English *megrim* and French 'migraine'. Another hypothesis is that migraine derives from the Latin word 'migrare' with respect to the aura. Nowadays, we accept the term migraine, derived from hemicrania, but it is undistinguishable from HC.

Medina and Diamond were probably the first authors to describe HC in 1981, in a subset of their 54 cluster headache variant patients who had strictly continuous unilateral headaches that were responsive to indomethacin, but they were classified as and coined as cluster headache variant [5].

 10.1586/ERN.09.85 ISSN 1473-7175

Box 1. IHS criteria for hemicrania continua.

A) Headache present for more than 3 months, fitting criteria B–D

B) All the following features:
Strictly unilateral headache
Daily and continuous, without headache free periods
Moderate intensity, with pain exacerbations

C) One of the autonomic features occurring during the exacerbation period:
Conjunctival injection and/or tearing
Nasal congestion and/or rhinorrhea
Ptosis or miosis

D) Complete response to indomethacin

E) Not associated to other disorder

The credit for the first description should be given to Sjaastad and Spierings when in 1984 they coined the term 'hemicrania continua' [6]. They reported two patients, a woman aged 63 years and a man aged 53 years, who developed a strictly unilateral headache that was continuous from onset and absolutely responsive to indomethacin. The man had associated autonomic features: redness, lacrimation and sensitivity to light; the woman had superimposed jabs and jolts. These cases were presented in September 1983 at the first International Headache Congress in Munich. In 1983, Boghen and Desaulniers also described a patient with a similar headache that they called 'background vascular headache responsive to indomethacin' [7]. A 49-year-old man had a 20-year history of left sided headache that radiated to the right with a sustained pressure-like quality. Associated with the headache was intermittent jabs of pain.

Approximately 130 cases of HC have been reported but there is still uncertainty regarding its clinical features; 97 were typical indomethacin-responsive cases, and 31 were patients with atypical features. Atypical features, including alternating side headaches (four cases), one patient with bilateral pain, 16 patients unresponsive to indomethacin, one patient associated with hemiplegic migraine and one evolving from cluster headache have been reported. Ten secondary cases, eight post-traumatic [8], one with a mesenchymal tumor [9], one with stroke [10] and another with HIV [11] have been reported.

In the majority of the cases, HC appears to have arisen *de novo*, without any identifiable trigger, although a number of secondary cases of HC have been described, associated with internal carotid artery dissection [12], pineal cyst [13], occuring postpartum [14], following head trauma [8], associated with pituitary tumor [15], ipsilateral mesenchymal tumor of sphenoidal bone involving clinoid process at base of skull [9], with HIV infection [11] and lung adenocarcinoma [16].

Valença *et al.* described a 47-year-old woman with a 3-year history of a continuum mild-to-moderate right-side headache, with exacerbations, associated with stabbing volleys of severe pain at the right orbit temporal region, right eye ptosis and tearing with conjunctival injection [10]. The pain was completely abolished with indomethacin (100 mg/day). The headache presentation was precipitated by a stroke and a right-side brainstem lesion was present at MRI. This case report shows anatomoclinical evidence of the involvement of brainstem structures in the pathophysiology of HC. Functional brain imaging demonstrated significant activation of the ipsilateral dorsal rostral pons in association with the headache attack of HC [17,18]. There was also a significant activation of the contralateral posterior hypothalamus and ipsilateral ventrolateral midbrain, which extended over the red nucleus and substantia nigra, and bilateral pontomedullary junction [17,18]. This is very interesting, since in the case reported by Valença *et al.* the brainstem lesion was ipsilateral to the side where the patient referred pain [10]. Another point to be discussed concerns the concomitant onset of both motor deficit and this particular type of headache, conferring a strong anatomoclinical correlation, indicating the pons as an area involved in the pathogenesis of the HC.

Clinical aspects

Hemicrania continua exists in continuous and remitting forms, the continuous form is more frequent. The continuous variety can be subclassified into an evolutive, unremitting form that arises from the remitting form and an unremitting form characterized by continuous headache from the onset. A chronic form evolving from a remitting form has been described [1].

Zukerman *et al.* reported in 1987 a patient with an unremitting form characterized by continuous headache from the onset [19].

The first case with a remitting course, reported by Sjaastad and Tjorstad in 1987, was the third HC patient reported in the literature [20]. The patient had a 7-year history of headache, in the first 4 years her headache lasted 1 day, followed by a 2–3 day pain-free period. In total she had 8–10 headache days per month. The pain-free period decreased over time; over the last 3 years she had daily headaches. There was a gradual transformation from the remitting to the continuous stage, similar to transformation of episodic into CM.

Centonze reported a patient who evolved from episodic cluster headache into the continuous stage of HC [21]. Pareja reported a patient who began in the continuous stage, but 5 years later, after discontinuing indomethacin, remained pain free [22]. This may have represented a continuous stage turning into a remitting course or was a spontaneous remission.

Bordini proposed three subtypes for HC. The continuous form, subdivided into continuous from onset, evolved from the remitting form (transformed), and remitting form [23]. At that point 18 cases were reported in the literature and analyzed, eight had the continuous form from the very beginning, eight had transition to the continuous stage, and two had the remitting form. Newman *et al.* reviewed the literature and added ten new cases, four in the remitting form and six in the nonremitting (continuous) form [24]. The remitting patients' bouts lasted from 1 to 6 months, separated by pain-free periods of 2 weeks to 6 months. In 1999 Espada reported nine new cases, eight continuous and one remitting [25]. Our case series was reported in 2001 [1], 34 cases met diagnostic criteria for HC, 30 patients in the continuous and four in the remitting form.

In total, 97 reports had available descriptions of their temporal pattern, 83 (85%) were reported in the continuous form and 14 in the remitting form (15%). In total, 64% of patients in the continuous form had it since the beginning and 36% of patients had the continuous evolved from the remitting form.

Two cases of remitting HC with a seasonal pattern have been reported [3,7]; a clinical history more focused on chronobiological variations is important in trigeminal autonomic cephalalgias (TACs) differential diagnosis since the temporal pattern is one of the important causes of HC misdiagnosis. One may not think of HC when a noncontinuous headache pattern occurs, or a remitting form is presented. Indomethacin should also be tried in those cases.

One of the essential features of HC is unilateral headache; however, bilateral and side-shifting cases have been reported. Pasquier (1987) reported the first patient with a bilateral, holocranial headache, continuous evolved from remitting, with complete response to 75 mg of indomethacin [26]. Iordanidis (1989) also reported a bilateral, but predominantly right-sided remitting case [27]. When the more consistent right-sided headache was extremely severe, the pain was felt on the left side, at 10–15% of the right-side severity. Newman (1992) reported a patient with a remitting form of HC with strictly unilateral attacks, which alternated sides [28]. Trucco (1992) also reported an alternating unilateral headache, which started as a remitting headache and evolved to continuous [29]. Other alternating HC cases were also reported.

These four reported cases were either remitting (two patients) or continuous evolving from remitting (two patients); none had the continuous form from the beginning. If we consider the previous ten remitting cases and 15 continuous cases evolving from remitting (total of 25), bilateral or side-shifting cases are present in 16% of this subgroup, which is not rare [30]. Ekbom reported side alternation in 10% of episodic cluster patients [31]. Bilateral cases have been reported in the literature in chronic paroxysmal hemicrania (CPH) [32] and in cluster headache, and a mechanism of failed contralateral suppression was proposed by Young and Rozen [33].

Bilateral or side-shifting cases of HC might occur. Bilateral HC may be underdiagnosed because one would not consider HC in a patient presenting with bilateral CDH. Hannerz reported an indomethacin test performed in a population of CDH patients with bilateral headaches who met diagnostic criteria for tension-type headache. An absolute response was found in three patients [34]. There may be a subgroup of patients with bilateral chronic headache who respond to indomethacin in the group of patients otherwise diagnosed as having CTH or even NDPH and CM. One may misdiagnose HC when those variants are not considered.

Regarding sex ratio, Bordini initially reported a female preponderance (5:1) in the first 18 cases reported [23]. Newman reported less female preponderance (1.8:1) [24] and Espada [25] found a slight male preponderance (1.25:1). Wheeler recently reported a strong female preponderance (29:1) [35]. Summarizing all the cases where gender data is available, there are 85 females and 32 males, with a 2.6:1 female:male ratio.

Associated symptoms in HC can be divided into three main categories: autonomic symptoms, 'jabs and jolts' and migrainous features. Autonomic symptoms include conjunctival injection, tearing, rhinorrhea, nasal stuffiness, eyelid edema and forehead sweatiness. These phenomena are not as prominent in HC as in cluster headache or CPH and are sometimes absent. The most common symptoms described are tearing, followed by nasal congestion, ptosis, conjunctival injection, rhinorrhea and eyelid edema. At least one autonomic symptom is usually observed in 75% of patients, the other 25% had more than one symptom. An important finding in the series by Peres *et al.* was a clear occurrence of the autonomic symptoms during pain exacerbations rather than the baseline headache [1]. It is important to consider that a minority of patients may not have autonomic features or have them very weak in severity: it is also one of the causes of misdiagnosis.

Sjaastad *et al.* reported, in the first two cases, specific tests for salivation, tearing, forehead sweatiness, facial temperature, and pupillometry after tyramine instillation and during the vagal test [36]. The only positive finding was late miosis (at 100 min) on the symptomatic side after instillation of tyramine, indicating probable subclinical sympathetic dysfunction on the symptomatic side. Antonaci *et al.* could not consistently replicate this finding in eight cases: only three cases showed this abnormality while all other cases were normal [37].

Jabs and jolts syndrome is described as sharp pain that lasts less than 1 min, occurs in patients with tension-type headache, migraine, cluster headache or in headache-free individuals, and responds to indomethacin [38]. Jabs and jolts pain occurs in HC and is more frequently observed in the exacerbation periods. The prevalence of this syndrome in the general population is reported as 30% [39]. It occurs in 26–41% of HC patients.

Migrainous features can ocurr in HC. Peres *et al.* reported 70.6% of their patients met International Headache Society (IHS) criteria for migraine in the exacerbation period while none did in the baseline period [1]. IHS diagnostic criteria for migraine could not be applied to previously reported cases because of lack of information. Nevertheless, 23 patients (50%) had at least one symptom, either nausea, vomiting, photophobia or phonophobia. Migrainous features can be associated with other headache disorders, including cluster headache, CPH and episodic paroxysmal hemicrania [40,41]. Peres (2006) report two patients with similar features: continuous unilateral headaches, side shifting accompanied by autonomic symptoms, visual aura, photo- and phono-phobia, and complete response to indomethacin [42].

Migrainous features can be considered as one of the main factors for HC misdiagnosis, together with temporal pattern. When a migrainous feature is present, it is natural that one may misdiagnose the disorder as a migraine, or migraine variant.

Neurological signs and symptoms have been reported in HC. In 1999 Evers, reported a patient with HC and attacks of hemiparesis, with a familial history of hemiplegic migraines [43]. Pasquier reported a patient with unilateral paresthesias [26], and Antonaci, in a case of HC secondary to a mesenchymal tumor, reported visual phenomenon described as dark spots [44].

HC with aura

Peres *et al.* reported four patients with a unique variant of HC: visual auras that preceded or accompanied the pain exacerbations [45]. Headache and visual symptoms were absolutely responsive to indomethacin. Auras only occurred preceding or during the pain exacerbation period, the time HC patients develop migrainous features. More probable is that auras can be an independent phenomenon that can accompany any form of primary headache disorder.

Multiple genes could be responsible for the aura and the primary headache, although it is improbable they would be unrelated. Aura-type symptoms have been described with headache disorders other than migraine, HC is one of those.

Responsiveness to indomethacin & other drugs

As reaffirmed recently, indomethacin is the drug of choice for paroxysmal hemicranias [46]. Response to treatment with indomethacin, in doses ranging from 25 to 300 mg/day, has been considered a *sine qua non* criterion to the correct diagnosis of HC [3,23,36,47].

In the case of the HC, how indomethacin would block the brain dysfunction/cerebrovascular regulation is still a matter of discussion. Indomethacin is a NSAID that has been found to cross the BBB, and it is known to inhibit the production of prostanoids through blockage of both constitutive and inducible isoforms of the COX enzyme, COX-1 and COX-2, respectively. Even though its half-life is approximately 4.5 h its anti-inflammatory effects last much longer. In mice its half-life in the serum and the brain was 10 and 24 h, respectively, following indomethacin oral administration (i.e., 2.4-times higher in cerebral tissue) [48]. Hypothetically, indomethacin might attenuate the headache by acting on brain centers and peripheral pain-related structures, simultaneously, through different mechanisms: changing the secretory processes of prostaglandin, neurotransmitters and neurohormones from brain tissues [49,50]; altering pituitary hormonal secretion, which may, in turn, directly or indirectly affect cerebral function [51], decreasing cerebral blood flow (CBF) via a vasoconstrictive effect [52]; exerting its classic anti-inflammatory actions; and via a binding at melatonin receptors owing to its similar chemical structure.

Indomethacin is a methylated indole derivative and a member of the arylalkanoic acid class of NSAIDs, which is frequently poorly tolerated with chronic use. Gastrointestinal (GI) side effects, such as nausea and dyspepsia, occur in approximately 3–9% of the patients and additional acid-suppression therapy is recommended [53].

Pareja *et al.* (2001) studies 26 patients with either HC or CPH under chronic use of indomethacin [53]. Relief of symptoms occurred within 3 days of treatment. They observed that, with time, 42% of patients experienced a decrease of up to 60% in the original beginning dose of indomethacin required to maintain the patient in a pain-free state. Adverse effects (mostly GI) were identified in six patients (23%), which were relieved with ranitidine. No major side effects were observed. The authors concluded that prolonged treatment with indomethacin has a good safety and tolerability profile with a reduction of up to 60% in the initial dose.

Drugs other than indomethacin that are reported to be helpful in HC include ibuprofen, aspirin, piroxicam β-cyclodextrin, celecoxib and rofecoxib. Kumar and Bordiuk reported a complete response to ibuprofen 800 mg three times daily [54]. Sjaastad and Antonaci found that of six patients, four responded to piroxicam β-cyclodextrin 20–40 mg daily [30]; one had a moderate response and one had no response. Peres reported a case responsive to rofecoxib [55]. Other classes of drugs have not been successful in controlling HC. Antonaci *et al.* reported lack of efficacy of sumatriptan in seven patients. Patients usually try many analgesics and all of them were reported to be of no benefit [56].

The dose for indomethacin response ranges from 50 to 300 mg daily. Kuritzky reported four cases unresponsive to 100 mg of indomethacin [57], but higher doses were not tried. Pascual reported other cases unresponsive to 225 mg [58]. The most common dose in our study was 150 mg daily.

A recently reported option for the diagnosis of indomethacin responsive headaches is the so-called 'indotest'[59]. In total, 12 patients with HC were given 50 mg of intramuscular indomethacin and some of them were given 100 mg on a second day. The time between indomethacin injection and complete pain relief was on average 73 min with the 50 mg injection and 61 min with the 100 mg injection. The pain-free period was 13 h after both the 50 and 100 mg injections. The authors suggest a standard dose of 50 mg of intramuscular indomethacin with observation up to 3 h, since relief occurred in all patients by 2 h.

Peres and Silberstein studied the response to two COX-2 inhibitors, celecoxib and rofecoxib, probably associated with fewer GI side effects, in the treatment of HC [60]. A total of 14 patients were treated, nine with rofecoxib, five with celecoxib. Patients were asked to discontinue indomethacin and start the selective COX-2 inhibitor if the headaches returned. All 14 patients had headache recurrence when indomethacin was stopped. Three patients in each group had a complete response to treatment. Secondary HC could be responsive to indomethacin even if the response faded after months. This aspect is key during the workout in HC diagnosis. Recently, Brighina *et al.* reported the cases of two patients who were successfully managed with topiramate 100–200 mg/day [61].

Melatonin is a pineal hormone with a chemical structure very similar to indomethacin. Recently, melatonin was shown to be effective for HC. Spears reports a case of HC in which attacks were successfully eliminated while taking melatonin 7 mg at bedtime after the patient was no longer able to tolerate indomethacin owing to GI side effects [62]. Rozen also report improvements in HC after treatment with melatonin [63].

Nocturnal exacerbations

Exacerbations are one of the most common features of HC, occurring in 74% of patients. Nocturnal exacerbations occur in HC and could result in a mistaken diagnosis of cluster or hypnic headache. In total, 30% of patients with HC had nocturnal exacerbations [1], sometimes more than once, and usually lasting 1–2 h. Conceivably, sleep might be related to the pathophysiology of HC.

Pathophysiology

The relative rarity of HC has made it difficult to study its pathophysiology. Pain pressure thresholds are reduced in patients with HC, as they are in CPH patients [37]. By contrast, orbital phlebography is relatively normal in HC patients in contrast to patients with CPH [64], although these findings are controversial [65]. Pupillometric studies have not shown an abnormality in HC [44], and studies of facial sweating have shown modest changes similar to those seen in CPH [66].

A relevant point to be distinguished is that functional imaging [17,18,67–69] has demonstrated with particular emphasis that the ontralateral brainstem (generally) mediates migraine while the ipsilateral brainstem mediates HC, suggesting that they are distinct headache entities, although presenting same common clinical features. Cerebral areas located outside the brainstem may also be involved in the genesis of primary headaches [17,18,67–69]. For example, the ipsilateral hypothalamus mediates cluster headache while the contralateral hypothalamus mediates HC.

In addition, electrode implantation in the periaquedutal gray region caused pain episodes in humans [70], suggesting that dysfunction in specific brainstem regions may trigger pain experience. Some of the patients reported abrupt, icepick-like, stabbing or rhythmic pounding pain, associated with transient visual symptoms, nausea or vomiting [70]. In this regard, dysfunction of brainstem nuclei and altered CBF in patients with migraine has been established [71], despite to the fact that during migraine attacks activation of the locus coeruleus and dorsal raphe nuclei was demonstrated by PET [68,69]. Thus, the brainstem plays an important role in the regulation of pain and CBF, since it contains antinociceptive and trigeminal nociceptive systems, and autonomic regulatory centers, which might be implicated in the regulatory mechanisms responsible for the unilateral autonomic events occurring in HC.

Prognosis

Espada *et al.* reported five men and four women who had HC [25] diagnosed using Goadsby and Lipton's proposed criteria [72] (eight continuous and one remitting with a mean age of onset of 53.3 years [range 29–69 years]). All nine patients had initial relief with indomethacin (mean daily dose 94.4 mg, range 50–150 mg). Follow-up was possible in eight patients. Indomethacin could be discontinued after 3, 7 and 15 months, respectively, and patients remained pain free. In total, three patients discontinued treatment because of side effects and had headache recurrence; two had relief with aspirin and two other patients continue to take indomethacin with partial relief.

Expert commentary: differential diagnosis of HC

Hemicrania continua is differentiated from cluster headache and CPH primarily by its continuous moderate pain and the lack of autonomic features between the painful exacerbations. HC can be aggravated by a C7 root irritation owing to a disc herniation [73]. A case of a mesenchymal tumor in the sphenoid bone in which the response to indomethacin faded after 2 months has also been reported [9]. These cases suggest that escalating doses or loss of indomethacin's efficacy should be treated with suspicion and the patient re-evaluated. The condition is also seen in noncaucasian populations [74].

The intermittent form of HC has features in common with migraine. Unilateral headache occurs in 60% of migraineurs and never alternates sides in 20% [75]. Both HC and migraine have a female preponderance and similar age of onset. The distribution of pain in both HC and migraine are similar, with a preponderance in the forehead and temporal regions. Nausea, photophobia and phonophobia are common in both HC and migraine. Migraine and HC patients report similar triggers: alcohol, weather changes, exertion, stress, odors, chocolate, bananas and cheese. Jabs and jolts (idiopathic stabbing headache) is common in migraine and universal in HC.

The continuous form of HC is in the differential diagnosis of the primary CDHs, which also includes CM, CTTH, and NDPH. CTTH is characterized by a relative lack of autonomic symptoms (including nausea, vomiting, photo-and phonophobia). These are seen in some, but not all, patients with HC. CM evolves out of episodic migraine headache and may retain many migrainous features, as do many cases of HC. CM is often seen when there is acute medication overuse, which can occur with HC. NDPH is defined as a new headache of sudden onset that occurs without a clear prior history of migraine; however, it often has migrainous features. This is similar to the continuous form of HC.

Chronic migraine, CTTH, CM, NDPH and HC may all be unilateral. The only factor that separates HC is indomethacin responsiveness. This responsiveness does not necessarily imply that a unique anatomic or physiologic defect causes the pain of HC. Indomethacin may ameliorate pain in all forms of CDH, but an exquisite sensitivity to indomethacin independent of the headache illness may indicate a unique pathophysiology for HC.

Nocturnal exacerbations may confound HC with cluster or hypnic headache. The short-lasting duration of attacks in cluster and hypnic headache is the differential for the diagnosis.

Five-year view

In a 5 year view of what has been published in the diagnostic challenge/misdiagnosis of the disorder HC we highlight three papers. One is the report of three HC cases with atypical features in which an acute intramuscular administration of indomethacin 50 mg (INDOTEST) was performed in a double-blind fashion [76]. In all the three cases INDOTEST predicted chronic responsiveness to indomethacin. This is important to consider because many patients present in the clinical setting with a different or atypical pattern, if one does not think of HC diagnosis, and indomethacin trial or the INDOTEST, as shown in this paper, would never be performed, and the diagnosis never performed correctly. The problem of the so-called INDOTEST is the unavailability of this product in many countries.

Another paper is the report of HC presenting as temporomandibular joint pain [77]. Patients with facial pain often present the most difficult diagnostic challenge to dental clinicians owing to the myriad of potential etiologies. Reports of HC masquerading

as dental or orofacial pain exist. Review of the literature reveals multiple patients describing the symptoms of this disorder as a toothache while one report included a patient who described temporomandibular joint pain. In this report, there were two additional cases of HC in patients whose chief complaints were centered on temporomandibular pain.

Unilateral photophobia or phonophobia in migraine was compared with TACs by Irimia *et al.* [78]. The authors wished to address whether there was lateralization of photophobia and phonophobia with the pain, and whether this had any clinical value in the differential diagnosis of TACs, HC and migraine. They screened 242 patients, 88 men and 154 women, aged 18–86 years (mean 43 years). Comparing the episodic primary headaches, unilateral photophobia or phonophobia was more common in TACs than migraine ($p < 0.0001$). Unilateral photophobia or phonophobia, or both, ipsilateral to the pain, was approximately three-times more common in HC patients compared with CM sufferers with unilateral pain. Furthermore, comparing chronic primary headaches, unilateral photophobia or phonophobia was more common in chronic cluster headache, chronic paroxysmal hemicrania and HC than CM, patients with medication overuse or NDPH ($c2.5: 117.3$; $p < 0.0001$). Patients with episodic and chronic cluster headache, chronic paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing syndrome or HC reported photophobia or phonophobia ipsilateral to the side of pain in more than 50% of the cases on average.

When clinicians consider a differential diagnosis that includes migraine, TACs and HC, certain clinical features, such as the presence of unilateral photophobia or phonophobia, may be helpful.

Financial & competing interests disclosure

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Hemicrania continua is a primary headache disorder more common than previously believed.
- Continuous unilateral headaches patients should receive an indomethacin trial early if not first in treatment.
- Atypical patients should be considered and a trial of indomethacin also performed.

References

1 Peres MF, Silberstein SD, Nahmias S *et al.* Hemicrania continua is not that rare. *Neurology* 57(6), 948–951 (2001).

2 Siberstein SD, Lipton RB, Solomon S, Mathew NT. Classification of daily and near-daily headaches: proposed revisions to the IHS criteria. *Headache* 34(1), 1–7 (1994).

3 Pareja JA, Vincent M, Antonaci F, Sjaastad O. Hemicrania continua: diagnostic criteria and nosologic status. *Cephalalgia* 21(9), 874–877 (2001).

4 Silberstein SD, Peres MF. Hemicrania continua. *Arch Neurol.* 59(6), 1029–1030 (2002).

5 Medina JL, Diamond S. Cluster headache variant. Spectrum of a new headache syndrome. *Arch. Neurol.* 38(11), 705–709 (1981).

6 Sjaastad O, Spierings EL. "Hemicrania continua": another headache absolutely responsive to indomethacin. *Cephalalgia* 4(1), 65–70 (1984).

7 Boghen D, Desaulniers N. Background vascular headache: relief with indomethacin. *Can. J. Neurol. Sci.* 10(4), 270–271 (1983).

8 Lay CL, Newman LC. Posttraumatic hemicrania continua. *Headache* 39(4), 275–279 (1999).

9 Antonaci F, Sjaastad O. Hemicrania continua: a possible symptomatic case, due to mesenchymal tumor. *Funct. Neurol.* 7(6), 471–474 (1992).

10 Valenca MM, Andrade-Valenca LP, da Silva WF, Dodick DW. Hemicrania continua secondary to an ipsilateral brainstem lesion. *Headache* 47(3), 438–441 (2007).

11 Brilla R, Evers S, Soros P, Husstedt IW. Hemicrania continua in an HIV-infected outpatient. *Cephalalgia* 18(5), 287–288 (1998).

12 Rogalewski A, Evers S. Symptomatic hemicrania continua after internal carotid artery dissection. *Headache* 45(2), 167–169 (2005).

13 Peres MF, Zukerman E, Porto PP, Brandt RA. Headaches and pineal cyst: a (more than) coincidental relationship? *Headache* 44(9), 929–930 (2004).

14 Spitz M, Peres MF. Hemicrania continua postpartum. *Cephalalgia* 24(7), 603–604 (2004).

15 Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. *Brain* 128(Pt 8), 1921–1930 (2005).

16 Eross EJ, Swanson JW, Dodick DW. Hemicrania continua: an indomethacin-responsive case with an underlying malignant etiology. *Headache* 42(6), 527–529 (2002).

17 Matharu MS, Cohen AS, McGonigle DJ, Ward N, Frackowiak RS, Goadsby PJ. Posterior hypothalamic and brainstem activation in hemicrania continua. *Headache* 44(8), 747–761 (2004).

18 Matharu MS, Goadsby PJ. Functional brain imaging in hemicrania continua: implications for nosology and pathophysiology. *Curr. Pain Headache Rep.* 9(4), 281–288 (2005).

19 Zukerman E, Hannuch SN, Carvalho Dde S, Fragoso YD, Jenger KA. "Hemicrania continua": a case report. *Cephalalgia* 7(3), 171–173 (1987).

20 Sjaastad O, Tjorstad K. "Hemicrania continua": a third Norwegian case. *Cephalalgia* 7(3), 175–177 (1987).

21 Centonze V, Attolini E, Campanozzi F *et al.* "Hemicrania continua": a new clinical entity or a further development from cluster headache? A case report. *Cephalalgia* 7(3), 167–168 (1987).

22 Pareja JA, Palomo T, Gorriti MA, Pareja J, Espejo J. "Hemicrania episodica": a new type of headache or a pre-chronic stage of hemicrania continua? *Headache* 30(6), 344–346 (1990).

23 Bordini C, Antonaci F, Stovner LJ, Schrader H, Sjaastad O. "Hemicrania continua": a clinical review. *Headache* 31(1), 20–26 (1991).

24 Newman LC, Lipton RB, Solomon S. Hemicrania continua: ten new cases and a review of the literature. *Neurology* 44(11), 2111–2114 (1994).

25 Espada F M-AF, Escalza I, Navas I, Iñiguez C, Mauri JA. Hemicrania continua: nine new cases. *Cephalalgia* 19, 442 (1999) (Abstract).

26 Pasquier F, Leys D, Petit H. "Hemicrania continua": the first bilateral case? *Cephalalgia* 7(3), 169–170 (1987).

27 Iordanidis T, Sjaastad O. Hemicrania continua: a case report. *Cephalalgia* 9(4), 301–303 (1989).

28 Newman LC, Lipton RB, Russell M, Solomon S. Hemicrania continua: attacks may alternate sides. *Headache* 32(5), 237–238 (1992).

29 Trucco M, Antonaci F, Sandrini G. Hemicrania continua: a case responsive to piroxicam-β-cyclodextrin. *Headache* 32(1), 39–40 (1992).

30 Sjaastad O, Antonaci F. Chronic paroxysmal hemicrania (CPH) and hemicrania continua: transition from one stage to another. *Headache* 33(10), 551–554 (1993).

31 Ekbom K. Clinical aspects of cluster headache. *Headache* 13(4), 176–180 (1974).

32 Pollmann W, Pfaffenrath V. Chronic paroxysmal hemicrania: the first possible bilateral case. *Cephalalgia* 6(1), 55–57 (1986).

33 Young WB, Rozen TD. Bilateral cluster headache: case report and a theory of (failed) contralateral suppression. *Cephalalgia* 19(3), 188–190 (1999).

34 Hannerz J. Chronic bilateral headache responding to indomethacin. *Headache* 40(10), 840–843 (2000).

35 Wheeler S. Clinical spectrum of hemicrania continua. Presented at: *52nd Annual Meeting of the American Academy of Neurology*. San Diego, California, USA 29 April–6 May 2000.

36 Sjaastad O, Spierings EL, Saunte C, Wysocka Bakowska MM, Sulg I, Fredriksen TA. "Hemicrania continua": an indomethacin responsive headache. II. Autonomic function studies. *Cephalalgia* 4(4), 265–273 (1984).

37 Antonaci F, Sandrini G, Danilov A, Sand T. Neurophysiological studies in chronic paroxysmal hemicrania and hemicrania continua. *Headache* 34(8), 479–483 (1994).

38 Sjaastad O, Russell D, Saunte C, Horven I. Chronic paroxysmal hemicrania. VI. Precipitation of attacks: further studies on the precipitation mechanism. *Cephalalgia* 2(4), 211–214 (1982).

39 Sjaastad O, Batnes J, Haugen S. The Vaga Study: an outline of the design. *Cephalalgia* 19(Suppl. 25), 24–30 (1999).

40 Young WB, Peres MF, Rozen TD. Modular headache theory. *Cephalalgia* 21(8), 842–849 (2001).

41 Castellanos-Pinedo F, Zurdo M, Martinez-Acebes E. Hemicrania continua evolving from episodic paroxysmal hemicrania. *Cephalalgia* 26(9), 1143–1145 (2006).

42 Peres MF, Masruha MR, Young WB. Side-shifting hemicrania continua with aura (migraine with aura with autonomic symptoms responsive to indomethacin?). *Cephalalgia* 26(8), 917–919 (2006).

43 Evers S, Bahra A, Goadsby PJ. Coincidence of familial hemiplegic migraine and hemicrania continua? a case report. *Cephalalgia* 19(5), 533–535 (1999).

44 Antonaci F, Sand T, Sjaastad O. Hemicrania continua and chronic paroxysmal hemicrania: a comparison of pupillometric findings. *Funct. Neurol.* 7(5), 385–389 (1992).

45 Peres MF, Siow HC, Rozen TD. Hemicrania continua with aura. *Cephalalgia* 22(3), 246–248 (2002).

46 May A, Leone M, Afra J *et al.* EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur. J. Neurol.* 13(10), 1066–1077 (2006).

47 Farias da Silva W VM. Hemicrania continua: a new case responsive to amitriptyline. *Neurobiology* 56, 155–158 (1993).

48 Dvir E, Friedman JE, Lee JY *et al.* A novel phospholipid derivative of indomethacin, DP-155 [mixture of 1-steroyl and 1-palmitoyl-2-{6-[1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl acetamido] hexanoyl}-sn-glycero-3-phosophatidyl [corrected] choline], shows superior safety and similar efficacy in reducing brain amyloid β in an Alzheimer's disease model. *J. Pharmacol. Exp. Ther.* 318(3), 1248–1256 (2006).

49 Valenca MM, Conte D, Negro-Vilar A. Diacylglycerol and phorbol esters enhance LHRH and prostaglandin E2 secretion from median eminence nerve terminals *in vitro*. *Brain Res. Bull.* 15(6), 657–659 (1985).

50 Negro-Vilar A, Conte D, Valenca M. Transmembrane signals mediating neural peptide secretion: role of protein kinase C activators and arachidonic acid metabolites in luteinizing hormone-releasing hormone secretion. *Endocrinology* 119(6), 2796–2802 (1986).

51 Picanco-Diniz DL, Valenca MM, Favaretto AL, Antunes-Rodrigues J. Stimulatory effects of adenosine on prolactin secretion in the pituitary gland of the rat. *Braz. J. Med. Biol. Res.* 35(7), 855–860 (2002).

52 Coyle MG, Oh W, Petersson KH, Stonestreet BS. Effects of indomethacin on brain blood flow, cerebral metabolism, and sagittal sinus prostanoids after hypoxia. *Am. J. Physiol.* 269(4 Pt 2), H1450–H14599 (1995).

53 Pareja JA, Caminero AB, Franco E, Casado JL, Pascual J, Sanchez del Rio M. Dose, efficacy and tolerability of long-term indomethacin treatment of chronic paroxysmal hemicrania and hemicrania continua. *Cephalalgia* 21(9), 906–910 (2001).

54 Kumar KL, Bordiuk JD. Hemicrania continua: a therapeutic dilemma. *Headache* 31(5), 345 (1991).

55 Peres MF, Zukerman E. Hemicrania continua responsive to rofecoxib. *Cephalalgia* 20(2), 130–131 (2000).

56 Antonaci F, Pareja JA, Caminero AB, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua: lack of efficacy of sumatriptan. *Headache* 38(3), 197–200 (1998).

57 Kuritzky A. Indomethacin-resistant hemicrania continua. *Cephalalgia* 12(1), 57–59 (1992).

58 Pascual J. Hemicrania continua. *Neurology* 45(12), 2302–2303 (1995).

59 Antonaci F, Pareja JA, Caminero AB, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua. Parenteral indomethacin: the 'indotest'. *Headache* 38(2), 122–128 (1998).

60 Peres MF, Silberstein SD. Hemicrania continua responds to cyclooxygenase-2 inhibitors. *Headache* 42(6), 530–531 (2002).

61 Brighina F, Palermo A, Cosentino G, Fierro B. Prophylaxis of hemicrania continua: two new cases effectively treated with topiramate. *Headache* 47(3), 441–443 (2007).

62 Spears RC. Hemicrania continua: a case in which a patient experienced complete relief on melatonin. *Headache* 46(3), 524–527 (2006).

63 Rozen TD. Melatonin responsive hemicrania continua. *Headache* 46(7), 1203–1204 (2006).

64 Antonaci F. Chronic paroxysmal hemicrania and hemicrania continua: orbital phlebography and MRI studies. *Headache* 34(1), 32–34 (1994).

65 Sjaastad O, Joubert J, Elsas T, Bovim G, Vincent M. Hemicrania continua and cervicogenic headache: separate headaches or two faces of the same headache? *Funct. Neurol.* 8(2), 79–83 (1993).

66 Antonaci F. The sweating pattern in "hemicrania continua". A comparison with chronic paroxysmal hemicrania. *Funct. Neurol.* 6(4), 371–375 (1991).

67 May A, Goadsby PJ. Hypothalamic involvement and activation in cluster headache. *Curr. Pain Headache Rep.* 5(1), 60–66 (2001).

68 Diener HC. How can PET scans help us understand headache mechanisms? *Cephalalgia* 19(Suppl. 23), 15–16 (1999).

69 Weiller C, May A, Limmroth V *et al.* Brain stem activation in spontaneous human migraine attacks. *Nat. Med.* 1(7), 658–660 (1995).

70 Raskin NH, Hosobuchi Y, Lamb S. *Headache* may arise from perturbation of brain. *Headache* 27(8), 416–420 (1987).

71 Sliwka U, Harscher S, Diehl RR, van Schayck R, Niesen WD, Weiller C. Spontaneous oscillations in cerebral blood flow velocity give evidence of different autonomic dysfunctions in various types of headache. *Headache* 41(2), 157–163 (2001).

72 Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. *Brain* 120(Pt 1), 193–209 (1997).

73 Sjaastad O, Stovner LJ, Stolt-Nielsen A, Antonaci F, Fredriksen TA. CPH and hemicrania continua: requirements of high indomethacin dosages – an ominous sign? *Headache* 35(6), 363–367 (1995).

74 Joubert J. Hemicrania continua in a black patient – the importance of the non-continuous stage. *Headache* 31(7), 480–482 (1991).

75 Selby G, Lance JW. Observations on 500 cases of migraine and allied vascular headache. *J. Neurol. Neurosurg. Psychiatry* 23, 23–32 (1960).

76 Baldacci F, Nuti A, Cafforio G *et al.* 'INDOTEST' in atypical hemicrania continua. *Cephalalgia* 28(3), 300–301 (2008).

77 Taub D, Stiles A, Tucke AG. Hemicrania continua presenting as temporomandibular joint pain. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 105(2), E35–E37 (2008).

78 Irimia P, Cittadini E, Paemeleire K, Cohen AS, Goadsby PJ. Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. *Cephalalgia* 28(6), 626–630 (2008).

79 Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders (Second Edition) *Cephalalgia* 24(Suppl. 1), 44 (2004).

Affiliations

- Mario FP Peres, MD, PhD, FACP
UNIFESP (Universidade Federal de São Paulo), São Paulo, Brazil
and
FMABC (Faculdade de Medicina do ABC), Al Joaquim Eugenio de Lima, 881 cj 708, 01403-01001 Sao Paulo, Brazil
Tel.: +55 113 285 5726
Fax: +55 113 285 5726
marioperes@yahoo.com
http://cefaleias.com.br/enxaqueca
- Marcelo M Valença, MD, PhD
Universidade Federal de Pernambuco, Division of Neurology and Neurosurgery, Department of Neuropsychiatry, Federal University of Pernambuco, 50670-50420 Recife, Pernambuco, Brazil
mmvalenca@yahoo.com.br
- André Leite Gonçalves, MD
UNIFESP (Universidade Federal de São Paulo), São Paulo, Brazil
AND
FMABC (Faculdade de Medicina do ABC), Al Joaquim Eugenio de Lima, 881 cj 708, 01403-01001 Sao Paulo, Brazil
Tel.: +55 113 747 3309
Fax: +55 113 285 5726
goncalvesnp@yahoo.com.br