Hemicrania Continua: Recent Treatment Strategies and Diagnostic Evaluation

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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. HC was once thought to be a rare headache disorder, but now many cases have been reported. It is an underecognized headache syndrome. HC can be of continuous or remitting form. Variants such as hemicrania continua with aura have been described, and secondary cases may occur. Indomethacin is the best treatment, although HC could respond to other nonsteroidal anti-inflammatory drugs, such as the selective cyclo-oxygenase-2 inhibitors.

Introduction

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) and migrainous features (photophobia, phonophobia, and nausea). HC is not triggered by neck movements, but tender spots in the neck may be present.

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

Hemicrania continua almost invariably has a prompt and enduring response to indomethacin. However, the requirement of a therapeutic response is problematic because it excludes the diagnosis of HC in patients who were never tried on, or who failed to respond to, indomethacin. Cases have been described that did not respond to indomethacin but met the phenotype; for this reason Goadsby and Lipton [2] have provided an alternate means of diagnosis. Silberstein *et al.* [3] also proposed diagnostic criteria for HC (Table 1).

Hemicrania continua takes precedence over the diagnosis of other types of CDH. CDH refers to the broad group of patients with very frequent headache (15 or more days a month with a duration greater than 4 hours). The major CDH subtypes are chronic (transformed) migraine (CM), HC, chronic tension-type headache (CTTH), and new daily persistent headache (NDPH) [3].

History of Diagnosis

The earliest recognition of a headache syndrome involving one side of the head is attributed to Aretaeus of Cappadocia (2nd century AD). However, Egyptian descriptions appear in papyri dating from 1500 BC. The physician Galen (131 to 201 AD) introduced the term "hemicrania" for unilateral headache. It was later transformed into the old English "megrim" and French "migraine." Nowadays we accept the term migraine, derived from hemicrania, but it is undistinguishable from hemicrania continua.

In 1981, Medina and Diamond [4] were the first modern authors to describe HC. They distinguished some patients in a subset of their 54 cluster headache variant patients who had strictly continuous unilateral headaches that were responsive to indomethacin.

The term "hemicrania continua" was coined by Sjaastad and Spierings [5] in 1984. 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 Con-

Table 1. Proposed criteria for hemicrania continua

Headache present for at least 1 month
Strictly unilateral headache
Pain has all 3 of the following present:
Continuous but fluctuating
Moderate severity, at least some of the time
Lack of precipitating mechanisms
Absolute response to indomethacin or one of the following autonomic features with severe pain exacerbation
Conjunctival infection
Lacrimation
Nasal congestion
Rhinorrhea
Ptosis
Eyelid edema
May have associated stabbing headaches
At least 1 of the following:
There is no suggestion of one of the disorders listed in groups 5–11 of the International Headache Society classification and diagnostic criteria
Such a disorder is suggested, but it is ruled out by appropriate investigations
Such disorder is present, but first headache attacks do not occur in close temporal relation to the disorder

Adapted from Silberstein *et al.* [3].

gress in Munich. In 1983, Boghen and Desaulniers [6] also described a patient with a similar headache that they called "background vascular headache responsive to indomethacin." 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 were intermittent jabs of pain.

Approximately 130 cases of HC have been reported, but there is still uncertainty about its clinical features. Ninety-seven were typical indomethacin-responsive cases, and 31 had atypical features. Atypical features, including alternating-side headaches (three patients), 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 [7], one with a mesenchymal tumor [8], and another with HIV [9] have been reported. summarizes typical cases and atypical cases.

Remitting/Continuous Course

Hemicrania continua exists in continuous and remitting forms. 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 to a remitting form has also been described.

The first case with a remitting course, reported by Sjaastad and Tjorstad [10] in 1987, was the third HC patient reported in the literature. The patient had a 7-year history of headache. In the first 4 years, her headache lasted 1 day, followed by a 2- to 3-day pain-free period. In total, she had 8 to 10 headache days per month. The pain-free period decreased over time, and 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 chronic migraine.

Centonze *et al.* [11] reported a patient who evolved from episodic cluster headache into the continuous stage of HC. Pareja *et al.* [12] reported a patient who began in the continuous stage, but 5 years later, after discontinuing indomethacin, remained pain free. This may have represented a continuous stage turning into a remitting course or was a spontaneous remission.

Bordini *et al.* [13] proposed three subtypes for HC: the continuous form, continuous from onset, and the remitting form. 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.* [14] reviewed the literature and added 10 new cases, four in the remitting form and six in the nonremitting (continuous) form. The remitting patient's bouts lasted from 1 to 6 months, separated by pain-free periods of 2 weeks to 6 months. Espada *et al.* [15] reported nine new cases, eight continuous and one remitting. Our case series was reported in 2001 [1••], with 34 cases meeting diagnostic criteria for HC (30 patients in the continuous and four in the remitting form).

Ninety-seven reports had available descriptions of their temporal pattern: 83 (85%) were reported in the continuous form and 14 (15%) in the remitting form. Sixty-four percent of patients with the continuous form had it since the beginning, and 36% of patients had the continuous form that evolved from the remitting form.

Side of Headache

One of the essential features of HC is unilateral headache; however, bilateral and side-shifting cases have been reported. Pasquier *et al.* [16] reported the first patient with a bilateral, holocranial headache, continuous evolved from remitting, with complete response to 75 mg of indomethacin. Iordanidis and Sjaastad [17] also reported a bilateral, but predominantly right-sided, remitting case. When the more consistent right-sided headache was extremely severe, the pain was felt on the left side at 10% to 15% of the right-side severity. Newman *et al.* [18] reported a patient with a remitting form of HC with strictly unilateral attacks that alternated sides. Trucco *et al.* [19] also reported an alternating unilateral headache that started as a remitting headache and evolved to continuous.

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 10 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 [20]. Ekbom [21] reported side alternation in 10% of episodic cluster patients. Bilateral cases have been reported in the literature in chronic persistent headache (CPH) [22] and in cluster headache, and a mechanism of failed contralateral suppression was proposed by Young and Rozen [23].

Bilateral or side-shifting cases of HC might occur. Because only a few cases have been reported, we consider such cases atypical and have not found such a patient in our clinic. Bilateral HC may be underdiagnosed because one would not consider HC in a patient presenting with bilateral CDH. Hannerz [24] 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. There may be a subgroup of patients with bilateral chronic headache who respond to indomethacin in the group of patients otherwise diagnosed as having CTTH or even NDPH and chronic (transformed) migraine.

Ratio Between Men and Women

Bordini *et al*. [13] initially reported a female preponderance (5 to 1 ratio) in the first 18 cases reported. Newman *et al*. [14] reported less female preponderance (1.8 to 1) and Espada *et al*. [15] found a slight male preponderance (1.25 to 1). Wheeler [25] reported a strong female preponderance (29 to 1). Summarizing all the cases where gender data is available, there are 85 female and 32 male patients (a 2.6 to 1 female to male ratio).

Associated Symptoms

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 chronic primary headache, and sometimes are 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. An important finding by Peres *et al*. [1••] was a clear occurrence of the autonomic symptoms during pain exacerbations, rather than the baseline headache.

Autonomic symptoms

Sjaastad *et al*. [26] reported specific tests for salivation, tearing, forehead sweatiness, facial temperature, and pupillometry after tyramine instillation and during the vagal test. The only positive finding was late miosis (at 100 minutes) on the symptomatic side after instillation of tyramine, indicating probable subclinical sympathetic dysfunction on the symptomatic side. Antonaci *et al*. [27] could not consistently replicate this finding in eight cases; only three cases showed this abnormality whereas all other cases were normal.

Jabs and jolts

Jabs and jolts syndrome is described as sharp pain, lasting less than 1 minute, and occurring in patients with tension-type headache, migraine, cluster headache, or in headache-free individuals, and responding to indomethacin [28]. 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% [29]. It occurs in 26% to 41% of HC patients.

Migrainous features

Migrainous features can occur in HC. Peres *et al*. [1••] reported 70.6% of their patients met Idiopathic Headache Score (IHS) criteria for migraine in the exacerbation period, whereas none did in the baseline period. 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 and CPH [30]. Neurologic signs and symptoms have been reported in HC. Evers *et al*. [31], in 1999, reported a patient with HC and attacks of hemiparesis with a familial history of hemiplegic migraines. Pasquier *et al*. [32] reported a patient with unilateral paresthesias, and Antonaci *et al*. [33], in a case of HC secondary to a mesenchymal tumor, reported visual phenomenon described as dark spots.

Hemicrania Continua with Aura

Peres *et al*. [34] reported four patients with a unique variant of hemicrania continua: visual auras that preceded or accompanied the pain exacerbations. Headache and visual symptoms were absolutely responsive to indomethacin. HC may be a migraine subtype, which is why aura can be associated with it. 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.

If aura is really an independent phenomenon, one gene could be responsible for the aura and another gene for the primary headache. This would help explain why aura-type symptoms have been described with headache disorders other than migraine.

Responsiveness to Indemethacin and Other Drugs

Indomethacin is a nonsteroidal anti-inflammatory drug that is frequently poorly tolerated. Drugs other than indomethacin that are reported to be helpful in HC include ibuprofen, piroxicam β-cyclodextrin, and rofecoxib. Kumar and Bordiuk [35] reported a complete response to 800 mg of ibuprofen given three times a day. Sjaastad and Antonaci [20] found that of six patients, four responded to 20 to 40 mg/d of piroxicam β-cyclodextrin. One had a moderate response and one had no response. Peres and Zukerman [36] reported a patient responsive to rofecoxib. Other classes of drugs have not been successful in controlling HC. Antonaci *et al*. [37] reported a lack of efficacy of sumatriptan in seven patients. Patients usually try many analgesics, and all of them were reported to be of no benefit. The dose for indomethacin response ranged from 50 to 300 mg/d. Kuritzky [38] reported four patients unresponsive to 100 mg/d of indomethacin, but higher doses were not tried. Pascual [39] reported other patients unresponsive to 225 mg/d of indomethacin. The most common dose in our study was 150 mg/d.

A recently reported option for the diagnosis of indomethacin-responsive headaches is the so-called "indotest" [40]. Twelve 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 73 ± 66 minutes with the 50-mg injection, and 61 ± 56 minutes with the 100-mg injection. The pain-free period after the 50-mg injection was 13 ± 8 hours, and 13 ± 10 hours after 100-mg injection. The authors suggest a standard dose of 50 mg of intramuscular indomethacin with observation up to 3 hours, because relief occurred in all patients by 2 hours.

Peres and Silberstein [41] studied the response to two cyclo-oxygenase (COX-2) inhibitors, celecoxib and rofecoxib, in the treatment of hemicrania continua. Fourteen patients were treated: nine with rofecoxib and 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.

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. Thirty percent of patients with HC had nocturnal exacerbations [1••], sometimes more than once, and usually lasting 1 to 2 hours. 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 [27,42]. In contrast, orbital phlebography is relatively normal in contrast with patients with CPH [43], although these findings are controversial [44]. Pupillometric studies have not shown an abnormality in HC [45], and studies of facial sweating have shown modest changes similar to those seen in CPH [46].

Prognosis

Espada *et al*. [47] reported five men and four women who had HC diagnosed using Goadsby and Lipton's proposed criteria [2] (eight continuous and one remitting, with a mean age of onset of 53.3 years [range of 29 to 69 years]). All nine patients had initial relief with indomethacin (mean daily dose of 94.4 mg, range of 50 to 150 mg). Follow-up was possible in eight patients. Indomethacin could be discontinued after 3, 7, and 15 months, respectively, and patients remained free of pain. Three patients discontinued treatment because of side effects and had headache recurrence; two had relief with aspirin. Two other patients continued to take indomethacin, with partial relief.

Differential Diagnosis

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 due to a disc herniation [48]. A case of a mesenchymal tumor in the sphenoid bone in which the response to indomethacin faded after 2 months has also been reported [8]. 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 seen in nonwhite populations [49].

The intermittent form of HC has features in common with migraine. Unilateral headache occurs in 60% of migraineurs and never alternates sides in 20% [50]. 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 chronic migraine (CM), CTTH, and NDPH. CTTH is characterized by a relative lack of autonomic symptoms (including nausea, vomiting, and photophobia 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 tension-type headache, 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.

Conclusions

Hemicrania continua is a primary headache disorder more common than previously believed. Continuous unilateral headaches should receive an indomethacin trial early, if not first, in treatment.

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Papers of particular interest, published recently, have been highlighted as:

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