CHAPTER 9

Hemicrania Continua

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Hemicrania continua (HC) is one of the primary chronic daily headache (CDH) disorders. It is characterized by a continuous, unilateral, moderately severe headache; exacerbations of severe pain associated with migrainous and autonomic features (tearing, conjunctival injection, ptosis); and complete responsiveness to indomethacin.

HC was once thought to be a rare headache disorder, but many cases have been reported. It is an underrecognized headache syndrome. 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.[1] Galen (131–201 AD) introduced the term "hemicrania" for unilateral headache. It was later transformed into the old English *megrim* and the French *migraine*. We now accept the term "migraine," derived from hemicrania. It differs from HC in its episodic nature.

Medina and Diamond probably were the first authors to describe HC in a subset of 54 patients who had cluster headache variants, as well as strictly unilateral, continuous headaches that were responsive to indomethacin.[2]

The term "hemicrania continua" was coined by Sjaastad and Spierings in 1984.[3] 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. In 1983, Boghen and Desaulniers described a patient with a similar headache that they called "background vascular headache responsive to indomethacin."[4]

HC is not that uncommon in clinical practice and should not be that rare in the general population. The prevalence of primary CDH in the general population is 4%. Epidemiologic studies never found HC in the population because the indomethacin trial has never been applied to the suspected cases. However, unilateral headache was found in 42% of chronic tension-type headache and 61% of chronic migraine patients.[5] HC has been reported in different countries and races. The first Japanese case was reported in 2002.[6] Wheeler also reported HC in African Americans.[7]

HC exists in continuous and remitting forms. The continuous variety can be subclassified into (1) an evolutive, unremitting form that arises from the remitting form and (2) an unremitting form characterized by continuous headache from the onset.

Ninety-seven patients had available descriptions of their temporal pattern; 83 (85%) were reported to be the continuous form and 14 (15%) the remitting form. Of patients who had the continuous form, 64% had it since the beginning and 36% of patients had the continuous form evolved from the remitting form.

A wide range of gender distribution has been reported. Bordini and colleagues reported a female preponderance (5:1) in the first 18 cases reported.[8] Newman and colleagues found less female preponderance (1.8:1),[9] and Espada and colleagues presented a slight male preponderance (1.25:1).[10] Wheeler reported the highest female preponderance (29:1).[11] Peres and colleagues found a 2.4:1 female to male ratio.[12] Summarizing all of the cases for which gender data are available, the female to male ratio is 2.6:1.

One of the essential features of HC is unilateral headache; however, some bilateral[13] or alternating side[14,15] cases have been reported. Ekbom reported side alternation in 10% of patients with episodic cluster headache.[16] Bilateral cases have been reported in the literature in chronic paroxysmal hemicrania[17] and in cluster headache, and a mechanism of failed contralateral suppression was proposed by Young and Rozen.[18]

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.[19] 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 chronic tension-type headache or even new daily persistent headache and chronic (transformed) migraine.

Associated symptoms present in HC can be divided into three main categories: autonomic symptoms, "jabs and jolts" (stabbing headaches) and migrainous features. Autonomic symptoms consist of conjunctival injection, tearing, rhinorrhea, nasal stuffiness, eyelid edema, and forehead sweating. These symptoms are not as prominent in HC as they are in cluster headache and chronic paroxysmal hemicrania. Symptoms of ocular discomfort, at times premonitory, have been described by patients with HC. Some patients report a feeling of sand in the eye, which may be specific for HC.[20] Peres and colleagues found autonomic symptoms to be more common in the exacerbation period compared with the baseline in HC.[12] At least one autonomic symptom was found in 75% of patients.

Jabs and jolts syndrome is described as sharp pain that lasts less than 1 minute; it occurs in patients with tension-type, migraine, and cluster headache or in headache-free individuals and responds to indomethacin. Jabs and jolts pain occurs in HC, more frequently in the exacerbation periods. Jabs and jolts syndrome is described in 26% of HC cases reported in the literature. Peres and colleagues found it in 41% of cases.[12] Its prevalence in the general population is 30%. Because of its low sensitivity and specificity, it should not be part of the diagnostic criteria for HC.

Migrainous features (nausea, vomiting, photophobia, or phonophobia) are common in HC, particularly in the exacerbation period.[21] The association between HC and visual auras was recently described.[22] Evers and colleagues reported a patient with HC and attacks of hemiparesis with a familial history of hemiplegic migraines.[23] Pasquier and colleagues reported a patient with unilateral paresthesias.[13] Little is known about the natural history of HC during pregnancy and reproductive life events. Hemicrania postpartum, a new HC variant, was recently reported.[24]

The pathophysiology of HC is unknown. It has been speculated that HC might be a migraine variant because many patients have headaches that have migrainous features. HC has been reported to be coexistent with familial hemiplegic migraine,[23] and HC with aura was recently described.[22] The mechanisms of indomethacin response are still unknown. Theories have included decreased cerebral blood flow, reduced cerebrovascular permeability, decreased cerebrospinal fluid pressure, an effect on melatonin secretion, and an antagonist effect on nitric oxide.[25]

Neuroimaging findings have improved our understanding of HC etiology. Matharu and colleagues studied seven patients with HC in two sessions.[26] In one session, patients were pain free after receiving indomethacin 100 mg intramuscularly. In the other session, patients were scanned with functional magnetic resonance imaging during baseline pain and when still in pain after receiving intramuscular placebo. The control group included seven age- and sex-matched nonheadache subjects. Scans revealed significant activation of the contralateral posterior hypothalamus and ipsilateral dorsal rostral pons, as well as activation of the ipsilateral ventrolateral midbrain, which extended over the red nucleus, the substantia nigra, and the bilateral pontomedullary junction. The scan exposed no obvious intracranial vessel dilation. This study demonstrated activation of various subcortical structures, in particular the posterior hypothalamus and the dorsal rostral pons. If posterior hypothalamic and brainstem activation are considered markers of trigeminal autonomic cephalgias and migrainous syndromes, then the activation pattern demonstrated in HC mirrors the overlapping clinical phenotype. However, the activation was opposite to that seen in trigeminal autonomic cephalgias and migrainous syndromes. In migraine, the brainstem is activated contralateral to the side of headache, but in HC, it is ipsilateral. In cluster headache, the hypothalamus is activated ipsilateral to the side of headache but contralateral in HC.

The management of HC is basically centered on indomethacin. Indomethacin is a nonsteroidal anti-inflammatory drug that is often poorly tolerated. Drugs other than indomethacin that are helpful in HC include ibuprofen, piroxicam β-cyclodextrin, and rofecoxib. Kumar and Bordiuk reported a complete response to ibuprofen 800 mg two times daily.[27] In 1992, Antonaci and Sjaastad found that four of six patients responded to piroxicam β-cyclodextrin 20 to 40 mg/d.[28] One patient had a moderate response, and one had no response.[28] Peres and Zukerman reported a case that was responsive to rofecoxib.[29] Other classes of drugs have not been successful in controlling HC. Antonaci and colleagues reported the lack of efficacy of sumatriptan in seven patients.[30] All analgesics were reported to be of no benefit. The dose for indomethacin response ranges from 50 to 300 mg/d. Kuritzky reported four cases that were unresponsive to 100 mg of indomethacin, but higher doses were not attempted.[31] Pascual reported other cases that were unresponsive to 225 mg.[32]

An outpatient test of indomethacin starts with administering 25 mg of the drug three times a day for the first 2 days and subsequently increasing the dose to 250 mg/d if necessary. An alternative to the indomethacin trial is the so-called "indotest." 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 66 to 73 minutes with the 50 mg injection and 56 to 61 minutes with the 100 mg injection. The pain-free period was 8 to 13 hours after the 50 mg injection and 10

to 13 hours after the 100 mg injection. The authors suggest a standard dose of 50 mg of intramuscular indomethacin with observation for up to 3 hours because relief occurred in all patients by 2 hours.[33]

Rozen recently reported that melatonin 6 to 12 mg at bedtime was an effective therapy for indomethacin-responsive headaches for one patient with HC and two patients with idiopathic stabbing headache.[34] Melatonin may be an alternative treatment for the indomethacin-responsive headaches; its molecular structure is similar to that of indomethacin,[35] and it tends to be more tolerable.

The differential diagnosis of HC includes other CDHs that can also be strictly unilateral. The continuous form of HC should be differentiated from the other primary CDH disorders (transformed migraine, chronic tension-type headache, and new daily persistent headache) by an indomethacin test. All patients who have strictly unilateral headaches should undergo an indomethacin trial to rule out a diagnosis of HC.

Chronic paroxysmal hemicrania does not have the continuous baseline headache found in HC; headache duration is shorter (2 to 45 minutes), and frequency is usually more than five a day. It is precipitated by neck movement, a feature that is not found in HC. Autonomic symptoms are more prominent in chronic paroxysmal hemicrania and cluster headache than in HC.

Three secondary cases have been reported. One patient had a mesenchymal tumor,[23] one had human immunodeficiency virus (HIV),[36] and one had a 2.5 cm adenocarcinoma lung mass.[37] HC can be aggravated by a C7 root irritation owing to a disk herniation.[38]

Bigal and colleagues compared two different diagnostic criteria for HC and found Goadsby and Lipton's to be more clinically useful.[39] The new classification in the International Headache Society's classification system includes diagnostic criteria for HC (Table 9–1).[40]

Espada and colleagues studied prognosis in five men and four women who had HC (eight continuous, one remitting).[10] All nine patients had initial relief with indomethacin (mean daily dose 94.4 mg; range 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 pain free. 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. Pareja and colleagues reported a patient who began in the continuous stage but 5 years later, after discontinuing indomethacin, remained pain-free.[41] This may have represented a continuous stage turning into a remitting course or a spontaneous remission. Pareja and colleagues studied HC and chronic paroxysmal hemicrania patients and found that 42% of patients experienced a decrease of up to 60% in the dose of indomethacin required to maintain a pain-free state; 23% of patients reported gastrointestinal complaints that were relieved with ranitidine.[42] Direct complications from the disease are not seen, but side effects from indomethacin (bleeding, renal failure, neuropathy) should be monitored.

Table 9–1 Diagnostic Criteria for Hemicrania Continua According to the International Classification of Headache Disorders, Second Edition[40]

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

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