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Chapter 102

Hemicrania Continua

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Hemicrania continua (HC) is a syndrome characterized by a unilateral, moderate, fluctuating, continuous headache, absolutely responsive to indomethacin. HC is relatively featureless except during exacerbations, when both migrainous symptoms and cranial autonomic symptoms may be present (31,38). "Hemicrania continua" was described by Sjaastad and Spierings (38). Relatively long-lasting unilateral headaches responsive to indomethacin were reported by Medina and Diamond under "cluster headache variant" (23), and Boghen and Desaulniers under "background vascular headache" (10).

International Headache Society (IHS) code number: 4.7 (17)
World Health Organization (WHO) code and diagnosis: G44.80 Other primary headaches

EPIDEMIOLOGY

The incidence and prevalence of HC is not known. It is regarded as a rare syndrome, but it may have been underdiagnosed (34,41).

HC has a female preponderance with a sex ratio of 2.4:1. The condition usually begins in adulthood, though the range of age of onset is 5 to 67 years (mean = 28 years) (34).

PATHOPHYSIOLOGY

The pathophysiology of HC is poorly understood. Cranial vasculature involvement has been investigated with orbital phlebography in six patients but only one patient had an abnormality consisting of bilateral narrowing of the ophthalmic veins, which may well be a nonspecific finding with unilateral pain (1).

Pain pressure thresholds are reportedly reduced in patients with HC (6), similar to paroxysmal hemicrania (PH) and cluster headache (CH) (7).

Pupillometric studies have shown no clear abnormality in HC (5), and studies of facial sweating have shown modest changes similar to those seen in PH (2). Most recently, a positron emission tomography (PET) study indicated significant activation of the contralateral posterior hypothalamus and ipsilateral dorsal rostral pons in association with the headache of HC. These areas corresponded with those active in CH and migraine, respectively. In addition, there was activation of the ipsilateral ventrolateral midbrain, which extended over the red nucleus and the substantia nigra, and of the bilateral pontomedullary junction. No intracranial vessel dilation was obvious (22). The data suggest that HC, like migraine and CH, is fundamentally a brain disorder and further that its pathophysiology may be completely unique. This would fit with the clinical presentation that has similarities to other primary headaches but indeed seems unique.

CLINICAL FEATURES

HC is a unilateral, continuous headache, without side shift, though rare bilateral cases (18,33,40) and a patient with unilateral, side-alternating attacks (24) have been described. The pain is mostly in the "anterior" area of the head, but not infrequently in the auricular/occipital area, or other regions of the head or neck can be affected (11). The pain is, typically, mild to moderate in intensity. The quality of pain is described as dull, aching or pressing, and generally lacking associated features (11,17,25,31,38).

In the majority of patients, exacerbations of severe pain are superimposed on the continuous baseline pain. These exacerbations can last from 20 minutes to several days. In one-third of patients, the headaches are nocturnal and are mistaken for CH or hypnic headache.

During exacerbations, the pain may be accompanied by a variable combination of ipsilateral autonomic features, commonly lacrimation and conjunctival injection. Ipsilateral ocular discomfort and nasal stuffiness may also occur (17). When present, autonomic signs are not as prominent in HC as in CH or PH. Furthermore, photophobia, phonophobia, nausea, and vomiting are common

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during exacerbations. In 26% to 41% of patients, primary stabbing headaches occur, predominantly during exacerbations (34). Jabs are frequent with HC, but they appear in other primary headaches as well.

There is a general paucity of factors that precipitate HC. Precipitants that are operative in other headaches generally seem to be of little relevance in HC; this includes stress, menses, alcohol, vasodilators, or exteroceptive stimuli acting on the tissues supplied by the trigeminal nerve. Furthermore, the headache is not aggravated by supine or other positions, Valsalva-like maneuvers, or physical activity. Neck movements do not trigger exacerbations, although occipital tenderness is present in 68% of patients (ipsilateral 44%, bilateral 24%) (25,34).

HC is continuous in the majority of patients, although some have an episodic or remitting form with distinct headache phases separated by pain-free remissions. HC is chronic from onset in 53%, chronic evolved from episodic in 35%, and episodic from onset in 12% (34). There is one case report of a patient who became episodic following a chronic onset (26).

International headache society criteria for HC (Revised International Classification of Headache Disorders—ICHD-II) (17):

A. Headache for >3 months fulfilling criteria B through 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 exacerbations of severe pain
C. At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain:
  1. Conjunctival injection and/or lacrimation
  2. Nasal congestion and/or rhinorrhea
  3. Ptosis and/or miosis
D. Complete response to therapeutic doses of indomethacin
E. Not attributed to another disorder (see Notes)

Notes:
History and physical and neurologic examinations do not suggest any of the disorders listed in groups 5 to 12, or history and/or physical and/or neurologic examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but headache does not occur for the first time in close temporal relation to the disorder.
Comment:
HC is usually unremitting, but rare cases of remission are reported. Whether this headache type can be subdivided according to length of history and persistence is yet to be determined.

Secondary Hemicrania Continua. Although there are no reports of clear-cut secondary HC, a C_7 root irritation due to a disc herniation has been noted to aggravate the condition (39). A patient with HIV developed HC, but causality is unclear (12). A case of a mesenchymal tumor in the sphenoid bone has also been reported in which the response to indomethacin faded after 2 months (8). This suggests that escalating doses or loss of efficacy of indomethacin should be treated with suspicion and the patient reevaluated. Eight cases of posttraumatic HC have been reported, although the temporal relationship of the trauma to the onset of HC was very variable (21).

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of HC include long-lasting unilateral headaches (e.g., unilateral chronic migraine, the syndrome of new daily persistent headache [NDPH], cervicogenic headache) and unilateral short-lasting headaches with oculofacial autonomic accompaniments (trigeminal autonomic cephalgias), particularly PH, the other headache absolutely responsive to indomethacin.

HC can be readily differentiated from chronic migraine and NDPH by the indomethacin responsiveness (14). It has been reported that patients with HC can develop a bilateral headache typical of rebound headaches if they overuse analgesics: There are three reports of what appeared to be chronic migraine with analgesia overuse, in whom upon withdrawing analgesics HC was uncovered. All three patients responded to treatment with indomethacin (42). Since HC is absolutely and permanently responsive to indomethacin, the main reason for HC sufferers to abuse analgesics and other medications is the lack of an appropriate diagnosis and treatment, or intolerance to indomethacin.

HC may be mistaken for cervicogenic headache but the absolute response to indomethacin and the absence of neck involvement and precipitating factors suffice in differentiating HC from cervicogenic headache (37). Indeed, anesthetic block of pericranial nerves, including the greater occipital nerve, often does not lead to any improvement in HC (3).

PH is so far the only other headache absolutely responsive to indomethacin, a fact that along with both strict unilaterality and clear female preponderance is similar to HC. The two headaches differ clearly in duration and intensity of pain (continuous/moderate in HC and severe/short lasting in PH) and also as regards the extent of oculofacial autonomic involvement (modest/variable in HC and dramatic/consistent in PH).

DIAGNOSIS

HC is diagnosed on the basis of clinical history, neurologic examination, and a therapeutic trial of indomethacin (17). A test dosage of 25 mg three times daily for 3 days is appropriate and, if ineffective, another 3-day course with 50 mg

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three times daily should be tried. We have seen some exceptional cases who require 75 mg three times daily and have taken 10 days to respond, but the vast majority of patients will respond within 24 hours. Many will respond within 8 hours with a standard oral dose of 75 to 150 daily (30). Intramuscular 50 to 100 mg indomethacin ("indotest") has been proposed as a diagnostic test for HC (4). Complete pain relief was reported to occur within 2 hours. The indotest has the advantage that the diagnosis can be rapidly established and when performed at the higher dose (100 mg) is likely to avoid the problem of an inadequate oral indomethacin trial. Although not widely used, it is likely to become the test of choice in unilateral primary chronic daily headache.

INVESTIGATION

A magnetic resonance imaging scan of the brain is a reasonable screening investigation to exclude secondary causes. Other tests, such as forehead sweating, pupillometry, algometry, and pericranial nerve blockade, have no diagnostic value in HC (27). Also, abnormal phlebograms are rather unspecific and do not distinguish HC from other similarly presenting headaches (1,27).

PROGNOSIS

As HC is a relatively recently described entity (38), its natural history is still being determined. It appears to be a chronic condition in most patients though several cases have been reported in whom indomethacin could be discontinued and the patients remained pain free (13,25). Patients should be advised to discontinue the indomethacin at least once every 6 months to test for possible remission. If not, the dose should be titrated to the minimum effective.

HC patients can expect an enduring response to indomethacin without developing tachyphylaxis, though between one-quarter to one-half develop gastrointestinal side effects (25,29). Indomethacin does not seem to alter the condition in the long term, though a significant proportion of patients can decrease the dose of indomethacin required to maintain a pain-free state (29).

MANAGEMENT

The treatment of HC is prophylactic. HC has a prompt and enduring response to indomethacin. The reported effective dose of indomethacin ranges from 25 to 300 mg daily (11,25,34,38). Dosage adjustments may be necessary to address clinical fluctuations. Skipping or delaying doses may result in headache relapse. Concurrent treatment with gastric mucosa protective agents should be considered as patients are expected to require long-term treatment.

Nonsteroidal antiinflammatory drugs other than indomethacin are generally of little or no benefit, although isolated case reports suggested efficacy with ibuprofen (19,25), piroxicam beta-cyclodextrin (36,40), naproxen (11), aspirin (13), the COX-2 inhibitor rofecoxib (35), and paracetamol with caffeine (11). Corticosteroids may be transiently effective.

Six patients have been described who had the clinical phenotype of HC but did not respond to indomethacin (20,32). This raises the question of whether there is a subset of patients with the underlying biology and clinical phenotype of HC who do not respond to indomethacin. If the mode of action of indomethacin involves interrupting the central pathogenetic mechanism of HC, then it is likely that all patients will respond to indomethacin and the indomethacin-resistant cases do not represent true HC (27). Several proposals have been made to solve the problem of whether the indomethacin response should be considered as a confirmatory feature (9,15,16) or as a compulsory diagnostic criterion (27,28). However, until the underlying pathophysiology of HC and the mode of action of indomethacin are better understood, this issue remains unresolved. According to the present diagnostic criteria of the IHS (17), the diagnosis of HC is accepted only in patients who are absolutely responsive to indomethacin.

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