Chapter 101

Hypnic Headaches

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HYPNIC HEADACHES

International Headache Society (IHS) code and diagnosis: 4.5 Hypnic headache
World Health Organization (WHO) Code: G44.80
Short description: Hypnic headache (HH) is a rare, recurrent, sleep-related, primary headache disorder. It usually begins after 50 years of age. The attack occurs at night when sleeping, waking the patient with a mild to moderate headache, severe in more than 20% of patients. Pain is bilateral in about two-thirds of cases. The attack usually lasts from 15 to 180 minutes, but longer durations have been described. Caffeine and lithium have been effective treatments in several reported cases. The pathophysiology of HH is unknown, but there is some evidence that it is related to rapid eye movement (REM) sleep.
Previously used terms: Hypnic headache syndrome, "alarm clock" headache

EPIDEMIOLOGY

Raskin first described hypnic headache in 1988 (35). Since then, more than 90 cases were reported in the literature (1–3,5–9,11–14,17–19,22–28,30–33,35–37,40–44). In the largest case study HH was diagnosed in 0.07% of all headache patients assessed annually at a specialty clinic (7). Although this is an estimated approximation of the true prevalence, it reflects the rarity of this syndrome.

PATHOPHYSIOLOGY

The exact pathophysiologic mechanisms of HH have not yet been elucidated. It has been postulated that HH may be the result of a chronobiologic disorder, serotonin and melatonin dysregulation, or a disturbance of REM sleep (5,8,9,17,31,33,37,38).

Raskin hypothesized that HH results from a disturbance of the mammalian biologic pacemaker of the brain residing within the suprachiasmatic nuclei (SCN) (34). Dysfunction of this "biologic clock," which generates circadian rhythms, has been linked to other phasic disorders such as bipolar illness, cluster headaches, and jet lag (34). A disturbance of the regulating system of the SCN could account for the clocklike regularity of headaches in HH.

Neuronal pathways exist between the SCN and the pain-modulating systems of the midbrain periaqueductal gray matter and dorsal raphe nuclei. These pathways and the mammalian biologic pacemaker are serotonergically modulated. Lithium carbonate, the agent most frequently reported to successfully treat this disorder, affects serotonin metabolism by downregulating serotonin receptors, thereby increasing serotonin release (39).

Dysregulation of melatonin has also been suggested as a putative mechanism of the syndrome. Melatonin is the main product of the pineal gland and is a marker of circadian rhythm. Melatonin modulates many neurobiologic functions such as cerebral vascular tone, serotonin neurotransmission, and inhibition of prostaglandin E_2 synthesis (17). With age, there is a decrease in the activity of the hypothalamic–pineal axis with a subsequent diminution of nocturnal secretion of melatonin. Lithium indirectly causes a rise in nocturnal melatonin levels by increasing serotonin production and tryptophan absorption, both melatonin precursors (4,20,21). Furthermore, melatonin therapy has been reported to abolish attacks in some patients with HH (5,8).

In that the headaches of HH occur exclusively during sleep, often during a dream, several investigators have postulated that the syndrome is a disorder of REM sleep. REM sleep is associated with decreased levels of serotonin, increases in cerebral blood flow, and dramatic reductions in the activity of the neurons within the dorsal raphe and locus ceruleus (37), an ideal setting for headache occurrence. In most patients with HH who underwent polysomnographic studies, attacks were associated with REM sleep

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(5,9,31); however, non-REM–related headaches have also recently been reported (22,41).

It is probable, given the differences in medication response and in polysomnographic studies, that more than one pathophysiologic mechanism is responsible for HH. Further investigations using sleep studies and functional neuroimaging may help to better elucidate the mechanisms of HH.

CLINICAL FEATURES

IHS diagnostic criteria (Revised International Classification of Headache Disorders, 2004 ICHD-II) (16):

A. Dull headache fulfilling criteria B through D
B. Develops only during sleep and awakens the patient
C. At least two of the following characteristics:
  1. Occurs ≥15 times per month
  2. Lasts ≥15 minutes after waking
  3. First occurs after the age of 50 years
D. No autonomic symptoms and no more than one of nausea, photophobia, or phonophobia
E. Not attributed to another disorder (i.e., intracranial disorders must be excluded. Distinction from trigeminal autonomic cephalalgias is necessary for effective management).

The onset of HH is usually late in life with a mean age at onset of 61 ± 10 years (range 30 to 83 years). A report of a 9-year-old girl with probable HH has been reported, although the headache frequency and age of onset did not meet IHS criteria (15). The average duration of the headache prior to diagnosis was 5 ± 8 years. The condition is more prevalent in women (65%) than in men.

The main characteristic of HH is that the pain awakens the patients during their sleep. The pain awakened 65% of the patients at a constant time interval during the night (hence, previously called "alarm clock" headache). Few patients (10%) reported that an identical headache might awaken them also during a daytime nap. The pertinent clinical characteristics of HH are summarized in Table 101-1.

The pain in HH is usually located anteriorly and less often involves the lateral aspects of the head, or is felt as a diffuse headache. On occasion it involves the occiput or radiates into the neck.

The duration of an untreated attack varies among patients and in between attacks. Usually the pain resolves within 1 to 2 hours (range 15 to 180 minutes), but longer attacks of up to 10 hours have been reported. The frequency of the attacks is high. More than four attacks per week occurred in 70% of the cases and about half of them had daily attacks (range one per week to six per night).

TABLE 101-1 Demographics and Clinical Characteristics of Patients With Hypnic Headache (n = 92)*

Gender	
F	56 (65%)
M	30 (35%)
Age at onset (years)	61 ± 10
Pain onset (hours after falling asleep)	
Within first 2	9 (13%)
2–4	50 (71%)
4 or more	9 (13%)
Intensity of pain	
Mild	3 (5%)
Moderate	34 (56%)
Severe	24 (39%)
Character of pain	
Dull/pressure	48 (55%)
Throbbing/pulsating	35 (40%)
Sharp/stabbing	4 (5%)
Side of the pain	
Unilateral	34 (38%)
Bilateral	56 (62%)
Associated features	
Nausea	15 (21%)
Photo- or phonophobia	11 (15%)
Lacrimation	4 (6%)
Ptosis	2 (2%)

*Not all data were available for every patient.

Autonomic phenomena do not seem to be a component of HH and their presence exclude the diagnosis of HH (16).

Although most of the patients tend to sit up in bed or got out of bed during the attack, only seven report that an upright position alleviated the pain. No triggers were identified as being capable of provoking HH. One patient reported that the headache started after a minor blow to the head; three patients considered alcohol as a trigger for HH attacks, while 19 patients did not.

A history of past headache has no influence on the development of HH. Out of 41 cases that provided past headache history, 23 (56%) had past headaches. These consisted of migraine (12 patients, 3 with aura), tension-type headache (6 patients), chronic daily headache (2 patients), cervicogenic headache (2 patients), and nonspecific hemicrania (1 patient).

The diagnosis of HH relies on the typical clinical features and the exclusion of an attributing disorder, particularly in cases with new-onset headache. Migraine and the trigeminal autonomic cephalalgias that might be related to sleep need to be excluded. As a primary headache, the neurologic examination and laboratory and imaging studies tend not to be revealing. Among 83 cases diagnosed with HH, computed tomography scan or magnetic resonance

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imaging (MRI) of the brain showed nonspecific white matter changes (two patients), vascular lacunar lesions (six patients), mild brain atrophy (three patients), or an incidental finding of meningioma (two patients). The relevance of these findings to HH is unclear and it might be a common result of investigations of this age group. Doppler ultrasound, electroencephalography, or neurophysiologic studies are normal.

Two reports of probable secondary HH have been described (10,29). In one, the patient had a 9-month history of typical HH, but also reported brief episodes of giddiness. A brain MRI revealed a large posterior-fossa meningioma. Its removal brought complete resolution of the headache (29). In the second report, HH-like headaches occurred in the setting of intracranial hypotension from an idiopathic cerebrospinal fluid leak. Headaches remitted following a spinal blood patch (10).

TREATMENT

Lithium was the first, and remains the most indicated, treatment for HH (8). Treatment is usually initiated with lithium carbonate 300 mg at bedtime and can be increased to 600 mg at bedtime within a week. Renal and thyroid function should be assessed prior to initiating therapy and periodically during treatment. Lithium serum concentrations should be monitored as well to avoid toxicity. Side effects include tremor, diarrhea, increased thirst, and polyuria.

Although lithium has higher efficacy rates than other medications, it is often poorly tolerated, especially by elderly patients, those most likely to be afflicted with this disorder. By reassuring the patients of the benign nature of the headache, some will choose to delay the usage of medications at all (7). Other agents that have been reported to effectively treat HH include bedtime doses of caffeine (40- to 60-mg tablet, or as a cup of coffee, or during the pain) (7,8), flunarizine 5 mg (8,25), and indomethacin 25 to 75 mg (6,8,17,18). Indomethacin appears to be of utility in HH when attacks are strictly unilateral (6). Treatment with melatonin, verapamil, and prednisone yielded mixed results, whereas tricyclic antidepressants and beta-blockers afford no benefit (3,8,34). Single reports of the usefulness of acetazolamide, gabapentin, and pizotifen cannot be adequately assessed (8,35).

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