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TUTORIAL

Focus on therapy of hypnic headache

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Abstract Hypnic headache (HH) is a primary headache disorder, which occurs exclusively during sleep and usually begins after 50 years of age. There are no controlled trials for the treatment of HH. We reviewed all the available papers, including 119 cases published in literature up to date, reporting the efficacy of the medications used to treat HH. Acute treatment is not recommended, since no drug proved to be clearly effective and also because the intensity and the duration of the attacks do not require the intake of a medication in most cases. As for prevention, a wide variety of medications were reported to be of benefit in HH. The drugs that were found to be effective in at least five cases are: lithium, indomethacin, caffeine and flunarizine. Lithium was the most extensively studied compound and demonstrated to be an efficacious treatment in 32 cases. Unfortunately, despite its efficacy, significant adverse effects and poor tolerability are not rare, mainly in elderly patients. Many patients reported a good response to indomethacin, but some could not tolerate it. Caffeine and melatonin treatments did not yield robust evidence to recommend their use as single preventive agents. Nevertheless, their association with lithium or indomethacin seems to produce an additional therapeutic efficacy. A course of lithium should be tried first, followed 3–4 months later by tapering. If headache recurs during tapering, a longer duration of therapy may be needed. If lithium treatment does not provide a significant response, indomethacin can be commenced as second-line approach. If these treatments prove to be ineffective or poorly tolerated, other agents, such as caffeine and melatonin, can be administered.

Keywords Hypnic headache · Therapy · Lithium · Indomethacin · Caffeine · Melatonin

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Background

Hypnic headache (HH) is a primary headache disorder, which occurs exclusively during sleep and usually begins after 50 years of age. Raskin first described the disorder in 1988 [1]; more than 100 cases have been subsequently reported. In the largest case series, HH was diagnosed in 0.07–0.1% of all headache patients assessed annually at a specialty clinic, reflecting the relative rarity of this condition [2]. HH usually begins late in life with a mean age at onset of 62 ± 11 years, with a range of 36-84 years. The mean duration of disease before diagnosis is 5 ± 7 years (range 0.1–35 years), suggesting that this condition is poorly recognized and perhaps underdiagnosed [2]. Three cases of probable HH in childhood and adolescence have been reported [3–5], although the occurrence at this age does not meet International Headache Society (IHS)

Table 1 ICHD-II criteria for hypnic headache

Description: attacks of dull headache that always awaken the patient from sleep
Diagnostic criteria
A. Dull headache fulfilling criteria B–D
B. Develops only during sleep, and awakens patient
C. At least two of the following characteristics
1. Occurs >15 times per month
2. Lasts ≥15 min after waking
3. First occurs after age of 50 years
D. No autonomic symptoms and no more than one of nausea, photophobia or phonophobia
E. Not attributed to another disorder

criteria. The condition is more prevalent in women (65%) than in men; in a personal large case series, we found a greater majority of females, accounting for 87.9% [6]. No case with a family history of HH has been reported so far. Table 1 lists the International Classification of Headache Disorders Classification, 2nd edition (ICHD-II) criteria for HH, that was included into group 4 (code 4.5), in the subheading of "Other primary headaches" [7].

Intracranial disorders must be excluded. Distinction from one of the trigeminal cephalalgias, in particular cluster headache, is necessary for effective management. The pain of HH is usually mild to moderate, but severe pain is reported by approximately 20% of patients. HHs occur in most cases at a consistent time each night, usually between 1:00 and 3:00 a.m., and may on rare instances occur during a daytime nap [2]. Pain is mainly bilateral, being unilateral in one-third of cases. It is usually localized anteriorly; on occasion it involves the occiput or radiates into the neck. The attacks usually last from 15 to 180 min, even if longer durations have been described. The frequency of attacks is usually high. More than 4 attacks per week occur in 70% of the cases and about half of patients have daily attacks [2]. Associated autonomic symptoms accompany the pain in approximately 8% of sufferers, and nausea, photophobia and phonophobia may rarely be present. The natural history of HH is not well known. It is assumed that it tends to be chronic unremitting, but only a few patients have been observed for at least 2 years. Some authors have classified HH into two different forms, chronic and episodic form. The episodic form is further subdivided into two types, episodic with no recurrence, and relapsing and remitting variety. Episodic form without recurrence may show spontaneous resolution or sustained remission even after withdrawal of the effective drug [5, 8, 9]. In view of previously published data, we proposed that HH be divided in two subtypes, chronic and episodic. We suggested that episodes of this disorder with remission periods of ≥1 month should be denoted by the term "episodic HH" and for those patients who have not experienced a remission over a period of at least 1 year, the disorder should be called "chronic HH" [8]. Some symptomatic cases have also been described, in which HH was linked to the onset of an intracranial lesion or disappeared after its removal. These cases were found to be secondary to a posterior fossa meningioma [10], a growth hormone-secreting pituitary tumour [11], and a nonfunctioning pituitary macroadenoma [12], respectively. Other cases of symptomatic HH related to obstructive sleep apnoea syndrome [13], ischaemic stroke in the midrostral upper pons [14], nocturnal arterial hypertension [15] and medication (ergotamine) overuse [16]. The exact pathophysiological mechanisms of HH have not yet been elucidated. It has been postulated that HH may be the result of a chronobiological disorder, serotonin, and melatonin dysregulation or a disturbance of rapid eye movement (REM) sleep. In most of the patients with HH who had polysomnographic studies, attacks were associated with REM sleep [2, 13, 17–22]; however, non-REM related HHs have also been reported [23–26]. In a recent paper reporting the results of polysomnography in 7 subjects whose HH attacks were recorded during the sleep studies, 3 patients had their headache attacks exclusively during non-REM sleep, 2 patients in REM sleep and the other 2 patients having both [9]. Furthermore, HH might be a chronobiological disturbance [27], because many patients experience the headache attack always at the same time in the night ("alarm-clock headache"). The most important brain structure for the endogenous circadian rhythm is the suprachiasmatic nuclei (SCN). The SCN have afferent and efferent projections with the periaqueductal grey and aminergic nuclei, which are the most important brainstem structures for pain modulation. With advanced age, the function of the hypothalamic-pineal axis, and in particular of the SCN, is diminished, and melatonin secretion is impaired or absent after the age of 60 years [2, 28–30]. The variety of drugs reported to be effective in HH (see below) also underscores the possibility that the pathophysiology might be heterogeneous. It is probable, given the differences in medication response and in polysomnographic studies, that more than one pathophysiological mechanism is responsible for HH. Further investigations using sleep studies and functional neuroimaging are necessary to better understand this syndrome.

Treatment

In the following paragraphs, we summarize the information collected from a systematic analysis of the international literature on the treatment of HH. We conducted a baseline literature search covering the period 1980–2009,

employing available electronic databases (National Library of Medicine, National Institute of Health, Embase) with the following medical search terms: hypnic headache, alarm-clock headache, nocturnal headache. Whenever available, chapters of book were also consulted and considered.

No controlled trials for the treatment of HH were found. Acute medications in the attack were tested only in a few patients. Notably, subcutaneous sumatriptan and oxygen inhalation, the treatments of first choice for cluster headache attacks, were not effective. Acetylsalicylic acid, caffeine and acetaminophen demonstrated, on average, only a mild efficacy for the acute relief of HH attacks. From the standpoint of preventive medications reported, lithium was used most frequently and also showed the best average efficacy. Lithium was the first treatment reported to be effective for HH [1]; this drug interacts with the pain-modulating system possibly involved in this disorder and seems to increase indirectly nocturnal production of melatonin. Moreover, lithium may exert an enhancing effect on cerebral serotonin functions. Lithium carbonate can be initiated at 300 mg at night and increased to 600 mg after 1 or 2 weeks if necessary [1, 9]. A good response was also noted with lower doses, even 150 mg at bedtime [8]. Out of the patients treated with lithium, this drug was discontinued in 5 cases [1, 31–33] despite its efficacy, due to significant adverse effects. Poor tolerability to lithium is not rare, mainly in elderly patients. Renal and thyroid function should be assessed before initiating therapy, and periodically during treatment. Serum lithium concentrations should be monitored as well to avoid toxicity. Side effects include tremor, diarrhoea, increased thirst and polyuria. Recently, a transient HH was described in a patient with bipolar disorder after the withdrawal of long-term lithium treatment [34]. Many other agents that have been reported to effectively treat HH include bedtime doses of caffeine (40–60 mg tablet, or as a cup of coffee), indomethacin, flunarizine, tricyclic antidepressants, verapamil, prednisone, topiramate, gabapentin, melatonin, benzodiazepines, pregabalin and acetazolamide. Curiously, of the patients treated with caffeine before bedtime, a disrupted sleep pattern was reported only in a few cases [27, 35]. The efficacy of indomethacin is of special interest because this drug is also effective in paroxysmal hemicrania and hemicrania continua [36]. It has been suggested that indomethacin may be helpful in those patients whose HH attacks are unilateral [31]. It was shown to be effective in extremely variable doses, ranging from 25 mg to 150 mg/day. Some patients who responded to indomethacin before bedtime developed daytime headaches, which resolved after indomethacin was discontinued. This phenomenon was termed as “the paradox of indomethacin”, whose most prominent side effect and reason for discontinuation (headache) is the very symptom for which it provides a remarkable therapeutic efficacy [31]. Other patients reported a good response to indomethacin, but could not tolerate it [21, 37]. Interestingly, the efficacy of topiramate, at the dose of 25 mg at bedtime and 100 mg/day was recently reported in two cases [33, 38]. A list of all drugs, both acute and prophylactic, that provided some benefit and their efficacy, as reported by the respective authors, is presented in Tables 2 and 3, respectively. In a personal large case series, including 33 patients, that was recently published as an abstract [6], we found that the most effective treatments were caffeine (7 cases), indomethacin (4 cases), melatonin (4 cases), lithium at low doses + caffeine (3 cases), lithium (1 case) and verapamil (1 case). The remaining 13 cases reported no benefit, refused the treatment or did not need any medication, since they were pain-free after an episodic period. Based on the literature review and our study results, we suggest a

Table 2 Different acute drug treatments in the published case reports on hypnic headache

Drugs	References	No. cases	Efficacy		
			Good	Moderate	None
Acetylsalicylic acid	[18, 39]	2	1	1	
Acetylsalicylic acid + caffeine	[27]	1	1		
Caffeine	[35, 41]	3	1	2	
Acetaminophen	[4, 19, 33, 40]	4	1	1	2
Sumatriptan 50 mg + caffeine	[27]	1	1		
Nimesulide	[19, 32, 33, 42]	4	1		3
Ibuprofen	[5, 32]	2	1		1
Triptans others than sumatriptan	[5, 32, 33, 39]	4		1	3
Ergotamine	[40]	1		1	
Sumatriptan 50–100 mg	[5, 19, 31, 33]	4			4
Oxygen inhalation	[5, 13, 18]	3			3
Indomethacin	[19, 33]	2			2
Sumatriptan 6 mg s.c.	[18]	1			1

Table 3 Different prophylactic drug treatments in the published case reports on hypnic headache

Drugs	References	No. cases	Efficacy		
			Good	Moderate	None
Lithium	[1, 8, 9, 13, 17, 19, 20, 23, 32, 33, 36, 38, 40, 41, 43–48]	47	32	10	5
Lithium + caffeine	[8, 35]	4	4		
Lithium + dothiepin + alprazolam	[40]	1	1		
Lithium + venlafaxine	[49]	1	1		
Lithium + amitriptyline	[41]	1		1	
Indomethacin	[5, 21–23, 27, 31, 32, 35, 37, 44, 46, 49–52]	22	10	3	9
Indomethacin + caffeine	[31, 41]	2	1	1	
Caffeine	[8, 18, 27, 31, 32, 39, 41, 50–52]	15	5	4	6
Caffeine + melatonin	[32]	2		2	
Flunarizine	[9, 17–19, 32, 33, 38, 41, 53, 54]	13	5	1	7
Flunarizine + melatonin	[54]	1	1		
Tricyclic antidepressants	[5, 18, 19, 23, 25, 26, 31, 33, 39, 41]	14	2	2	10
Prednisone	[8, 13, 27, 32, 38, 42]	7	2	1	4
Verapamil	[18, 19, 31, 32]	5	2		3
Verapamil + amitryptiline	[18]	1	1		
Topiramate	[33, 38]	2	2		
Gabapentin	[23, 32, 52]	3	1	1	1
Melatonin	[31, 52]	4	1		3
Benzodiazepines	[13, 19]	2	1		1
Atenolol 25 mg	[27]	1	1		
Pregabalin	[52]	1	1		
Acetazolamide	[37]	1	1		
Botulinum toxin type A	[39]	1	1		
Cinnarizine	[32]	1	1		
Ergotamine + phenobarbital	[27]	1	1		
Acetylsalicylic acid + caffeine	[27]	1	1		
Eszopiclone	[55]	1	1		
Clorazepate + venlafaxine + valproate	[34]	1	1		
Oxetorone	[48]	8		8	
Atenolol 50 mg	[32, 41]	3		2	1
Propranolol	[5, 13, 19, 33]	7			7
Antidepressants others than tricyclics	[5, 13, 23, 39, 49]	6			6
Pizotifen	[19, 23, 32, 33, 38]	4			4
Methysergide	[13, 23]	3			3
Valproate	[5, 19, 33]	3			3
Ergotamine	[31]	1			1
Acetylsalicylic acid	[31]	1			1

practical approach to the management of HH, which is shown in Fig. 1. Although some patients may specifically ask for an acute treatment, this is not recommended, since no drug showed to be clearly effective; furthermore, the mild-to-moderate intensity and the short duration of the attacks do not require the intake of acute medications in most cases. The attacks subside spontaneously in a relatively short time, almost never exceeding the duration of 2–3 h. Moreover, the intensity is mild to moderate in the majority of cases. The patients themselves are more concerned with the prevention of the headaches, rather than with the treatment of the single attacks. As for prophylaxis, a course of 300–600 mg lithium should be tried first, on some instances in association with caffeine and/or melatonin, followed, 3–4 months later, by tapering. If headache recurs during tapering, a longer duration of therapy may be needed. The treatment with caffeine and in particular with melatonin alone did not yield robust evidence to

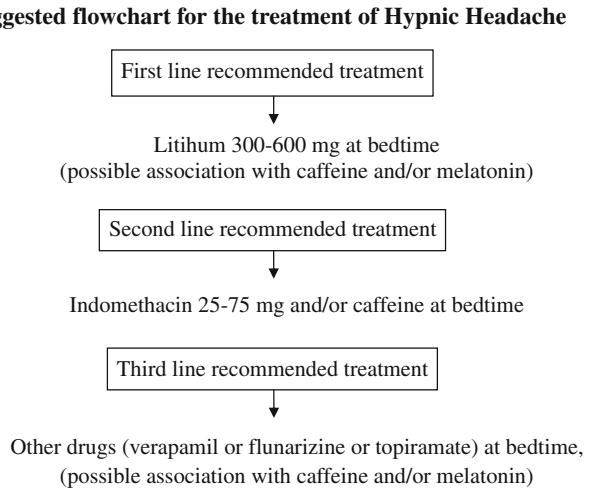

Fig. 1 Suggested approach to the management of HH

recommend their use as single preventive agents. Their association with the recommended medications (i.e. lithium and indomethacin) seems to produce an additional overall therapeutic efficacy. Anyway, some patients responded completely to caffeine given alone at bedtime. If lithium treatment does not provide a significant response, as second line approach indomethacin can be commenced, at a dose ranging from 25 to 75 mg at bedtime; based on the above remarks, caffeine can also be tried, alone or in combination with indomethacin. If these treatments prove to be ineffective, other medications, such as verapamil, flunarizine or topiramate, can be administered. These drugs are also recommended when lithium and indomethacin are contraindicated or are related to significant side effects.

Conflict of interest None.

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