REVIEW

Hypnic headache

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INTRODUCTION

Hypnic headache is a rare episodic headache syndrome first described by Raskin in 1988. It has also been called 'clockwise headache' or 'alarm-clock headache' (Newman *et al.* 1990). More than 80 similar cases have been reported and our recent systematic review of all published cases described the typical clinical picture and treatment options (Evers & Goadsby 2003). Characteristically, many times a month, a dull pain wakens the patient from sleep, it lasts for more than 15 min, tends to start over the age of 50, but it does not have the autonomic features of cluster headache (Table 1).

So far everyone has assumed that hypnic headache is an idiopathic headache disorder. Diagnostic criteria were first proposed in 1997 (Goadsby & Lipton 1997) and hypnic headache is now included in the revised version of the headache classification of the International Headache Society (IHS) (Headache Classification Subcommittee 2004).

CLINICAL FEATURES

A total of 94 published cases could be analysed for this review. We will describe the various clinical and pathophysiological features separately to give an overall impression of the varieties of hypnic headache (Table 2).

Demographic data

The mean age at onset is 62 years (range 30–84). There is a slight female preponderance – about 3 : 2. The headaches had been occurring before diagnosis for about five years, ranging from less than 1 year to 35 years, showing that the condition is poorly recognized and perhaps underdiagnosed. In 16 patients the hypnic headache episodes resolved spontaneously but in most cases the episodes of headache continued more persistently. There was no case with a family history of hypnic headache. Normally therefore the disorder occurs as a chronic form, although episodic forms, by which we mean spontaneous prolonged periods without attacks, have been described (Lisotto *et al.* 2004).

The frequency of patients with hypnic headache is not really known. It was reported as the main diagnosis in 0.07% of all patients in the Headache Clinic at the Mayo Hospital (Dodick *et al.* 1998) and in a German supraregional headache outpatient clinic, hypnic headache

was diagnosed in about 0.1% of all headache patients (Evers *et al.* 2003).

Clinical data

The average intensity of pain was mild in 4%, moderate in 60%, and severe in 37%. There were no relevant changes of intensity, except as a result of medication, during the course of the disease. The most prominent character of the pain was dull in 57%, throbbing/pulsating in 39%, and sharp/stabbing in 4%. The pain was bilateral in 62% of the cases and always one-sided in 38% (13% right, 15% left, 9% either side). The localization of the typical headache was fronto-temporal (including periorbital) in 45%, posterior in 3%, and diffuse in 52%.

Untreated, the attacks lasted about 1.5 h (range 15–600 min). They occurred about once every 24 h (range one per week to six per night). In 4% of the patients, the onset of the first attack in the night was 30–60 min after falling asleep, and in 9% between 60 and 120 min after falling asleep. Most of the patients (75%) had the onset of their first attack between 120 and 480 min after falling asleep, and only 12% of the patients had the first attack later than four hours after sleep onset. In 60% of the patients, the onset of an attack occurred at much the same time, most often about 3 h after falling asleep, between 1 and 3 o'clock in the morning.

Data on concomitant symptoms during the headache were described in only a few patients. Eight out of the 94 patients had autonomic symptoms and so fulfilled the IHS criteria for cluster headache or chronic paroxysmal hemicrania (lacrimation in four patients, in part with nasal congestion or rhinorrhea, and ptosis in two patients). However, none of these patients fulfilled the *complete* IHS criteria for cluster headache or chronic paroxysmal hemicrania. Nausea was reported in 22% of the patients during the headache, none reported vomiting. Mild photophobia, or phonophobia, or both, were reported in 5% of the patients.

In eight patients, it was explicitly noted that the headache was worse when lying flat. These patients experienced marked relief of the headache when they got into the upright position. In fact, nearly all the patients got up during the headache and were active, there was no report of headache aggravation by physical activity. Four patients reported headache episodes during daytime sleep, whereas three patients had consistently no headache at all during their daytime nap.

Table 1 International Headache Society diagnostic criteria for hypnic headache

A	Dull headache fulfilling criteria B–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 min 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

Note: Intracranial disorders must be excluded. Distinction from one of the trigeminal autonomic cephalalgias is necessary for effective management.
Comment: The pain is usually mild to moderate, but severe pain is reported by some patients. Pain is bilateral in about two thirds of cases. The attack usually lasts from 15 to 180 min, but longer durations have been described. Caffeine and lithium have been effective in several reported cases.

Table 2 Demographic and clinical features of the patients with hypnic headache analysed in this review. The data are given as percentages or as arithmetic means with standard deviations (range in brackets). Data were not available from all patients for every variable

Sex	
Men	37%
Women	63%
Age at onset (years)	62 ± 12 (30–84)
Duration of attacks (min)	100 ± 116 (15–600)
Frequency of attacks per 24 h	1.2 ± 0.8 (1/7–6)
Intensity of pain	
Mild	4%
Moderate	60%
Severe	37%
Character of pain	
Dull	57%
Throbbing/pulsating	39%
Sharp/stabbing	4%
Side of headache	
Unilateral	38% (13% right, 15% left, 9% either)
Bilateral	62%
Localization	
Fronto-temporal	45%
Posterior	3%
Diffuse	52%
Concomitant symptoms	
Nausea	22%
Photo-/phonophobia	5%
Lacrimation	6%
Ptosis	3%

In three patients, alcohol was a trigger for the hypnic headache attacks, but in 19 alcohol did not have any influence on the occurrence of attacks. Other triggers were not reported

Neurophysiological and neuroradiological findings

An MRI and a CT scan of the brain was performed in 51 and 56 cases, respectively. In 14 cases, no brain imaging at all was reported. There were no pathological findings except non-specific white matter changes including lacunar lesions in six cases, meningioma in two cases, and mild atrophy in two cases. All neurophysiological examinations (EEG, Doppler ultrasound, evoked potentials) were normal. Data on blood analysis were given in a minority of patients and there were no abnormalities which could not be explained by a concomitant disorder or disease independent of the hypnic headache.

Sleep recordings

Polysomnography was performed in 21 patients (Dodick 2000; Molina Arjona *et al.* 2000; Evers *et al.* 2003; Pinessi *et al.* 2003; Kocasoy *et al.* 2004; Manni *et al.* 2004; Patsouros *et al.* 2004). The headache attacks always occurred during REM sleep in nine patients and during sleep stage 2 or 3 in five; the remaining seven patients did not have a headache attack during polysomnography. In all nine patients with REM-associated hypnic headache, the attack occurred during the first REM stage for the night. Two of these patients had multiple REM-associated attacks per night (Fig. 1). Another 11 patients, who did not have polysomnography, reported onset of headache attacks during dreams, four of them during nightmares or vivid dreams

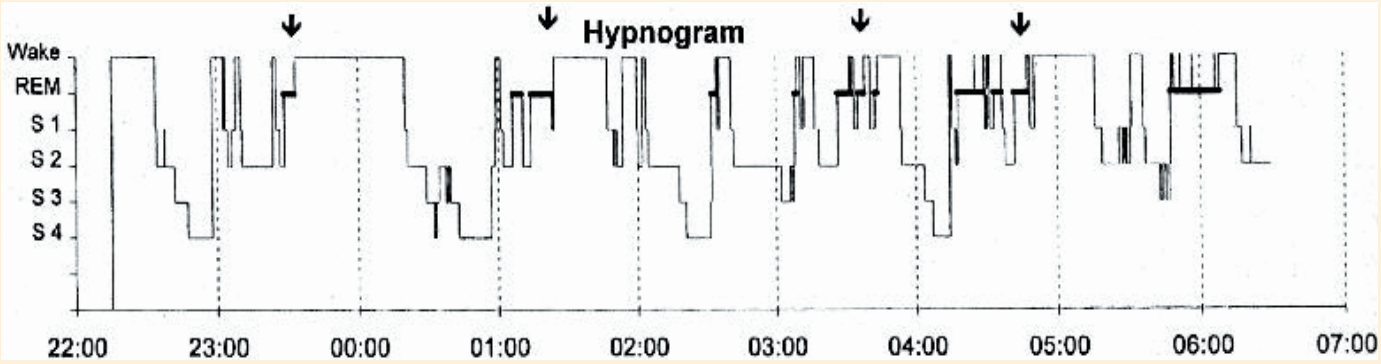
Sleep quality was normal except for decreased sleep efficiency (i.e. amount of sleep during time in bed) of down to 60% in eight patients who had polysomnography. There were no sleep apnoeas recorded in any patients, although snoring was observed in 12. Oxygen saturation was decreased mildly down to about 90% in three patients and down to about 70% in another two patients for a few minutes. Two patients showed periodic limb movement during a night with a hypnic headache attack. Interestingly, one patient had remission of hypnic headache for 3 months after travelling across time zones (Martins & Gouveia 2001).

Comorbidity

In 44 cases, a previous headache history was explicitly sought. Fifteen cases had had migraine, three of them with aura. In seven cases, episodic tension-type headache was reported. Two had chronic daily headache, one unspecified hemicrania, and one cervicogenic headache. In 18 cases, no headaches at all were reported in the past.

Comorbidity was noted in a number of patients, most frequently hypertension in 12 patients (in 27 patients hypertension was explicitly excluded). In two patients, smoking of at least 20-pack-years was described, but in the majority of patients no information on smoking habit was given. The remaining conditions reported were atrial fibrillation, diabetes mellitus (twice), depression or dysthymia (four times), coronary heart disease (four times), malignant neoplasm (five times), obstructive sleep apnoea syndrome (two without polysomnography), stroke, Meniere's disease, hiatus hernia, tuberculosis, essential tremor (twice), epilepsy (twice), cystic kidneys, HIV infection without AIDS, pituitary microadenoma, multiple sclerosis, and Sjögren's syndrome. There was no pattern of diseases or disorders typically associated with hypnic headache.

Figure 1 Hypnogram of a patient with multiple attacks of hypnic headache every night. The arrows denote the onset of an attack (always at the beginning of REM sleep).



MANAGEMENT

Medication in the attack was tried in only a few patients. Notably, sumatriptan subcutaneously and oxygen inhalation, the drugs of first choice for the treatment of cluster headache, were not effective. Only aspirin gave moderate relief of hypnic headache in some patients.

For prophylactic drug treatment, lithium was tried the most frequently and also showed the best efficacy in a daily dose between 150 and 600 mg. Several authors suggested it should be the drug of first choice. Similar efficacy was found for indomethacin, flunarizine and caffeine. The efficacy of indomethacin is of special interest since this drug is effective in paroxysmal hemicrania and hemicrania continua (Goadsby & Lipton 1997). Indomethacin has been suggested to be helpful in hypnic headache only if the attacks are unilateral (Dodick *et al.* 2000). No other drugs provided any benefit for the prevention of hypnic headache attacks more than the expected placebo effect. In particular, antidepressants and betablockers were not useful. A list of all the drugs tried in at least two patients, and their efficacy as reported by the respective authors, is presented in Table 3 . There appear to have been no randomised controlled trials, nor even any n-of-1 trials, and so the formal evidence for the various suggested prophylactic strategies is not particularly good

Non-drug therapies, such as sleep restriction or physiotherapy, were not reported. Continuous positive airway pressure (CPAP) was completely successful in one patient (Dodick 2000), continuous oxygen supply was tried in three patients but without any benefit (Evers *et al.* 2003).

PATHOPHYSIOLOGY

The pathophysiology of hypnic headache is speculative because there have been no experimental studies. Not surprisingly, it has been debated whether hypnic headache is a particular subtype of cluster headache. However, only the time features of hypnic headache support this hypothesis. There is no strict unilaterality and no obligatory cranial paraympathetic activation in hypnic headache, as is usually observed for the trigeminal-autonomic cephalalgias. It has been suggested that hypnic headache is on a spectrum (with respect, to laterality and the presence of autonomic symptoms) overlapping with other primary headache disorders (Dodick *et al.* 1998). Interestingly, some cases of cluster headache would fulfil the criteria for hypnic headache, but not vice versa, if the absence of autonomic symptoms are omitted from the criteria.

Most striking is the observation that the onset of hypnic headache attacks is during REM sleep which has been observed in all but one of the patients studied with polysomnography, or assumed from the history of dreaming. Although the number of cases is too small for any final conclusions, this observation suggests that pain processing structures are activated during REM sleep. This might be a similar mechanism as, for instance, in Schenck's syndrome when the pyramidal motor system is activated or disinhibited during REM sleep. Some authors have described nightly headache attacks due to hypertension, which might also occur during REM sleep

Table 3 Different drug treatments mentioned in the case reports on hypnic headache (number of patient reports in brackets). Only the drugs tried in at least two patients are presented. The efficacy is classified according to the statements of the respective authors.

	Efficacy		
	None	Moderate	Good
Acute drugs			
Aspirin (9)	3	5	1
Triptans (8)	6	1	1
Ergotamine derivatives (6)	3	2	1
Acetaminophen (5)	3	2	–
Oxygen inhalation (4)	4	–	–
Nimesulide (2)	1	–	1
Prophylactic drugs			
Lithium (49)	5	5	39
Caffeine (24)	9	4	11
Indomethacin (22)	9	5	8
Tricyclic antidepressants (21)	20	1	–
Betablockers (15)	14	–	1
Non steroidal anti-inflammatories* (12)	8	4	–
Verapamil (9)	6	1	2
Melatonin (9)	4	2	3
Flunarizine (7)	3	–	4
Anticonvulsants (not gabapentin) (6)	6	–	–
Prednisone (6)	3	1	2
Antidepressants (not tricyclic) (5)	5	–	–
Benzodiazepines (4)	3	–	1
Pizotifen (4)	3	–	1
Methysergide (3)	3	–	–
Gabapentin (3)	–	2	1
Clonidine (3)	2	1	–
Opiates (2)	2	–	–
Barbiturates (2)	1	–	1

*Including ibuprofen, diclofenac, naproxen, ketoprofen.

(Cugini *et al.* 1992), and due to low oxygenation during REM sleep (Dodick 2000).

It is known that the different types of sleep apnoea coincide with morning or nocturnal headache (Aldrich & Chauncey 1990; Loh *et al.* 1999). However, in the case series with polysomnography in hypnic headache, no obstructive sleep apnoea syndrome has been found (Evers *et al.* 2003; Pinessi *et al.* 2003; Manni *et al.* 2004). Only one patient improved after CPAP and oxygen supplementation (Dodick 2000), three patients did not (Evers *et al.* 2003).

It has been suggested that hypnic headache might be a REM sleep disorder due to a disturbance of the sleep-related physiology of the brain stem (Dodick 2000). During REM sleep there is no activity in the dorsal raphe and locus coeruleus (Somers *et al.* 1993). These areas are, together with the periaqueductal grey matter, essential parts of the human antinociceptive system and it might be that in hypnic headache their function is impaired during REM sleep. However, frequent onset of headache attacks during REM sleep has also been reported for migraine and episodic cluster headaches. Thus, the association between REM sleep and hypnic headache is not specific.

Hypnic headache might be a chronobiological disturbance since many patients experience their headache attack always at the same time in the night ('alarm-clock headache'). The most important brain structures for the endogenous circadian rhythm are the suprachiasmatic nuclei, which function as a pacemaker for this rhythm. The nuclei have afferent and efferent connections with the periaqueductal grey, which is one of the most important mid-brain structures for anti-nociception. With advanced age, the function of the hypothalamic-pineal axis, and in particular of the suprachiasmatic nuclei, is diminished and melatonin secretion is impaired. This can also be observed in cluster headache (Leone *et al.* 1995). There are several biological functions of melatonin, which could explain how decreased levels of this hormone would lead to the development of headache (Dodick *et al.* 1998). That hypnic headache is a chronobiological disorder is also supported by the efficacy of lithium, which is of therapeutic value in other chronobiological disorders such as cluster headache and affective disorders. Lithium indirectly increases the level of melatonin (Chazot *et al.* 1987; Lewis *et al.* 1990; Pablos *et al.* 1994) and may thus affect the pathophysiology of hypnic headache. In one patient with hypnic headache, melatonin seemed to be effective (Dodick 2000).

Neither relevant structural brain lesions nor metabolic dysfunction could be detected in any of the reported cases. This suggests that hypnic headache is an idiopathic headache disorder rather than a symptomatic headache. However, a symptomatic headache cannot conclusively be discounted since there are no systematic studies of metabolic changes or underlying sleep disorders. Furthermore, there is no evidence for a genetic predisposition for hypnic headache, which would be expected of an idiopathic headache disorder. Admittedly, the number of cases is too small to exclude genetic mechanisms. The variety of drugs reported to be effective in hypnic headache also underscores the possibility that the pathophysiology might be heterogenous.

RELATED CONDITIONS

There are idiopathic headache conditions similar to hypnic headache in the sense that they appear only in close temporal relationship to sleep. Besides the nocturnal occurrence of migraine, cluster headache, and paroxysmal hemicrania, which will not be reviewed here, there are the exploding head syndrome and turtle headache.

The exploding head syndrome was first described in 1920 (Armstrong-Jones 1920). Since then, single cases (Evans & Pearce 2001; Jacome 2001), case series (Pearce 1989) and a review (Green 2001) have been published. The exploding head syndrome is the sensation for some seconds that an explosive noise has occurred in the head, which wakens the patient from sleep. There is no actual pain. The attacks tend to occur during the transition from wakefulness to sleep. Polysomnographic studies have shown these attacks occur during all sleep stages, including REM sleep (Sachs & Svanborg 1991). Interestingly, like hypnic headache, most patients are over 50 years of age. The short duration of the

CONCLUSIONS

- Hypnic headache belongs to the group of idiopathic headache syndromes.
- As there are no accompanying autonomic symptoms in most cases, and are very mild in the remaining cases, hypnic headache does not belong to the so-called trigeminal autonomic cephalalgias but must be classified as one of the miscellaneous headaches unassociated with structural lesions (group 4 of the IHS classification).
- The diagnostic work-up of patients presenting with the typical symptoms of hypnic headache should include a thorough history and neurological examination. In atypical cases, MRI scan of the brain, in particular to exclude lesions of the brain stem, is indicated.
- In some cases, polysomnography might be helpful to distinguish hypnic headache from REM sleep behaviour disorder or other parasomnias.
- The most successful prophylactic management is lithium, at least 150 mg per day and, to a lesser extent, indomethacin 100 mg or caffeine given in the evening. Typically, we use caffeine first (1–2 cups), as if it works it does not disturb sleep in these patients and has no serious adverse effects.
- Acute treatment of hypnic headache attacks is generally impossible due to their short duration; triptans, oxygen and nonsteroidal anti-inflammatory drugs do not seem to give any relief.
- It is important to distinguish hypnic headache from other idiopathic headache disorders – in particular from cluster headache and from paroxysmal hemicrania, which can also occur exclusively in the night – because of the different treatment options.
- The patient should be informed about the harmless nature of the condition and of the good prognosis although in most cases long-term treatment is necessary.

exploding head symptoms and the absence of real pain or headache distinguish the syndrome from hypnic headache.

Turtle headache occurs in the morning after awakening and going back to sleep, and was first described in 1972 (Gilbert 1972). The headache is bilateral and only occurs if the patient pulls the bed covers over his or her head, or retracts his or her head under the blankets, like a turtle retreating under its carapace. It has been suggested that hypoxia is the underlying cause (Gilbert 1982) and so this should be regarded as a symptomatic headache.

SYMPTOMATIC CASES

According to the IHS criteria for hypnic headache, intracranial lesions have to be excluded. This is difficult because older patients frequently have nonspecific intracranial abnormalities such as leucoaraiosis or cerebral atrophy, but these cannot be regarded as the cause of hypnic headache. However, some cases have been described in which the hypnic headache disappeared after removal of, or was linked to the onset of, an intracranial lesion. Peatfield & Mendoza (2003) described a 54-year-old female who suffered from typical hypnic headache and was diagnosed with a posterior fossa meningioma. After removal of the tumour, the hypnic headache attacks stopped. Another symptomatic case was a 72-year-old male with hypnic headache attacks occurring after an ischaemic stroke in the midrostral upper pons, the site of the pontine reticular formation (Moon *et al*. 2003). In a 43-year-old female, the diagnostic work-up of a typical hypnic headache revealed a non-specific inflammatory meningeal lesion in the region of the foramen lacerum (Vieira-Dias & Esperance 2002). At this time the patient was also diagnosed as having HIV infection with involvement of several cranial nerves.

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