Report of eight new cases of hypnic headache and mini-review of the literature

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Accepted for publication: November 29, 2002

Summary

Hypnic headache is a rare condition first described by Raskin in 1988. This headache is not included in the first edition of the International Headache Society classification (IHC 1st Edition). We describe eight new Italian hypnic headache cases and consider our findings in the light of literature data.

Our cases do not completely fulfil the diagnostic criteria for the syndrome proposed in 1997 by Goadsby and Lipton: four of our patients reported an attack duration longer than 60 minutes (ranging from 3 to 10 hours) and five reported unilateral pain. These data are in line with an analysis of all 61 cases published in the literature to date, which reveals a pain duration of over 60 minutes in 45.9% of the cases and unilateral attacks in 36%.

Hypnic headache will be included in the fourth chapter (Other Primary Headaches) of the revised edition of the above-mentioned classification (IHC 2nd Edition).

KEY WORDS: Hypnic headache, nocturnal headache, primary headache, sleep

Introduction

Hypnic headache is a rare, benign disorder first described by Raskin (1) in 1988, as a “curious sleep-related headache syndrome”. Onset of this headache form – attacks occur exclusively during sleep and at a regular time – is generally after the age of 50 years.

This headache was not included in the first edition of the International Headache Society classification (2), but Goadsby and Lipton suggested diagnostic criteria for it in 1997 (3). The subcommittee designated to revise the fourth chapter (Other Primary Headaches) of the International Headache Society classification has decided to include hypnic headache in this chapter of the second edition (4). We describe eight new Italian hypnic headache cases and consider our findings in the light of literature data.

Case reports

Patient 1

A 61-year-old woman (L.R., housewife) presented with an 11-year history of headache. The pain awakened the patient every night, at 4-5 a.m. (after five sleep hours) and was generalized, fixed in quality, severe in intensity and associated with slight nausea. It was not exacerbated by physical activity. Duration of the attack was not known, because the patient always took symptomatic treatment (acetylsalicylic acid 1 gram or indomethacin 50 mg are effective in 15-20 minutes). Before the menopause (52 years), L.R. had suffered from menstrual migraine and episodic tension-type headache. She has a thyroid nodule. Physical and neurological examinations gave normal findings, as did routine blood tests and brain CT scan. Her blood pressure was within normal limits.

Treatment with melatonin 3 mg and caffeine 60 mg was begun; after three months, her headache severity had decreased from severe to mild, but the frequency was unchanged. The patient is now in her third year of the disease; she often prevents attacks by setting an alarm clock to go off after four hours of sleep.

Patient 2

A 61-year-old woman (L.C., shift nurse) had a nine-year history of left-sided headache that awakened her from sleep after 2-5 sleep hours (bedtime: 10-11 p.m.). The pain was throbbing or fixed, moderate or severe in intensity, without associated symptoms and lasted for 3-6 hours. Attacks occurred 15 times per month (having gradually increased from an initial frequency of 2-3/month). L.C.’s attacks were unresponsive both to triptans and to non-steroidal anti-inflammatory drugs. In the past she had undergone treatment with beta-blockers (atenolol 50 mg/day), calcium antagonists (flunarizine 10 mg/day, verapamil 240 mg/day), and pizotifen (1 mg/day), all without benefit. She had also taken lithium carbonate...
Patient 4

A 61-year-old man (A.L., ex-shift-worker, retired in 1993) presented with a 7-year history of nocturnal headache. The attacks, occurring about every 7 days, usually awakened him from sleep at 3-4 a.m., but recently (for the past 3 months) they had been awakening him at 5:30-6:30 a.m. He usually goes to bed at midnight. The pain was boring in quality, moderate in intensity, left-side located, without associated symptoms and had a duration of 8-9 hours. Nimesulide (100 mg) reduced only the intensity of the pain (but not the frequency of the attacks). The patient’s general and neurological examinations were within normal limits. He presented a history of acoustic trauma and mild snoring. An ear-nose-throat evaluation revealed turbinate hypertrophy and nasal septal deflection. The patient had a normal brain CT scan.

He was treated for one year with gabapentin (600 mg/day) and the intensity of the pain decreased (from moderate to mild). He suggested he gradually discontinue the gabapentin and take caffeine 60 mg with melatonin 5 mg. After one month, the patient reported improved efficacy of nimesulide, which stopped the pain; furthermore, the attacks were once more occurring at 3-4 a.m., as they had done initially. After one-year of therapy, the pain intensity has been reduced from moderate to mild; nimesulide (100 mg) aborts attacks in 30 minutes; but the headache still awakens the patient at 3-4 a.m. and the attack frequency is unchanged (4 attacks/month).

Patient 5

A 58-year-old woman (C.B., housewife) presented with a 4-year history of headache that awakened her every night at 5:30-6 a.m. (bedtime: 11 p.m.). The pain was right-side located, fixed in quality, moderate-severe in intensity, without associated symptoms, and had a duration of 60 minutes. Headaches could be prevented from occurring by 25 mg of oral indomethacin, taken at bedtime. Prior to the menopause (52 years), C.B. suffered from menstrual migraine. Her medical history was otherwise unremarkable and her general physical and neurological examinations were normal.

In April 2001, she started treatment with cinnarizine 30 mg and caffeine 75 mg at bedtime; over next three months she experienced only 5 attacks and after seven months reported a further reduction in attack frequency. After one year of therapy, she reported a frequency of just one attack in 2-3 months. Therefore, the caffeine was withdrawn, leaving only the cinnarizine, and there was no modification of the headache features. She is now going to reduce the cinnarizine dose.

Patient 6

A 69-year-old man (L.A., ex-driver, retired in 1986) reported a 2-year history of headache, which awakened him from sleep at 00-00.30 a.m. (bedtime: 9-10 p.m.). Attacks occurred every 5-6 nights and lasted for 8-10 hours. The pain was throbbing, right-temporal-located, severe in intensity, and without associated symptoms; it was not aggravated by physical activity. Ibuprofen (200 mg) and tramadol (100 mg) were ineffective. The patient had a fifteen-year history of chronic obstructive pulmonary disease (smoking-related); in January 2001 he had suffered an episode of bronchitis followed by acute pulmonary oedema, which necessitated his hospitalisation. Respiratory function tests revealed an obstructive pattern and analysis of arterial blood gases gave low PO₂ (74.8 mmHg / n.v. 80-100 mmHg) and normal PCO₂ (41.8 mmHg / n.v. 35-45 mmHg) values. The next pneumological examination revealed a gradual normalisation of the respiratory parameters. Echocardiography revealed right ventricular failure. He was being treated with theophilline (400 mg/day). His physical and neurological examinations were normal, as was his brain CT scan. In July 2002, he began therapy, 60 mg of caffeine at bedtime.

Patient 7

An 84-year-old man (D.L., retired) reported a 1-year history of daily sleep headache, which awakened him every night at 2 a.m. The pain, severe and throbbing, was located in the fronto-temporo-parietal region bilaterally and vertex, and was associated with nausea. The attacks lasted for 120 minutes and forced the patient to get up. For 20 years, D.L. had suffered from chronic obstructive lung disease without hypercapnia (treated with inhalation of disodium chromoglicate, beclometasone, oxymetopium). The patient had a history of ischaemic heart disease with arterial hypertension (successfully treated with amlodipine) and hyperlaemia, diagnosed in 1990. His physical examination showed signs of obstructive bronchopathy. Neurological examination revealed postural bilateral tremor in both upper limbs, mild generalised extrapyramidal hypertonia, moderate dystarthis. CT scan of the brain revealed multiple areas of lacunar-type hypodensity in deep brain regions bilaterally and low attenuation of periventricular white matter.
Hypnic headache: eight new cases

The patient was treated with 450 mg of lithium carbonate for just seven days, discontinuing therapy due to tremor increase and consciousness disorders (nocturnal confused state with agitation). During this week of treatment he did not experience any attacks. The patient did not tolerate caffeine therapy (a cup of coffee at bedtime), which caused insomnia. D.L. died of myocardial ischaemia in 2001.

**Patient 8**

A 67-year-old woman (B.I., retired) presented with a 15-year history of headache, that awakened her every night at 3-5 a.m. The attacks sometimes awakened the patient while she was dreaming. The pain was dull, moderate-severe in intensity, located in the vertex and the occipital region bilaterally, associated with slight nausea and invariably obliged her to get up, with pain improving in 15-60 minutes. No local autonomic symptoms were present. She has no history of any other kind of headache. B.I.’s general and neurological examinations were normal. The patient underwent brain CT scan (normal), 24-hour monitoring of blood pressure (one episode of tachycardia with raised blood pressure, not associated with the attack), blood tests (normal), ECG (right bundle block), and roentgenogram of the cervical spine (spondylosis with marginal osteophytosis and discopathies at C4-C7 levels).

The patient was treated with 600 mg of lithium carbonate without improvement of the headache; also 50 mg of indomethacin taken before going to bed was ineffective; she started (for 15 days) a cycle of prednisone (25 mg), experiencing only a slight reduction in the headache intensity. Finally she was treated with caffeine at bedtime (100 mg), and had a complete remission of the attacks. The dose was reduced to 60 mg and the headache did not reappear, but any attempt to withdraw the drug resulted in a relapse of the nocturnal attacks.

**Discussion**

To date, 61 cases of hypnic headache syndrome (Table I, see over) have been described in the literature (a figure that includes reports in abstracts from congress proceedings). This is a rare syndrome, first described in 1988 by Raskin (1) as a late-onset headache that awakens patients from nocturnal/diurnal sleep at a regular time. According to Raskin the main characteristics of hypnic headache are: brief duration, generalised or bilateral pain, and absence of associated autonomic symptoms. Goadsby and Lipton (3) proposed the diagnostic criteria (Table II, see over), based on the existing literature (8 cases reported).

Table III (see over) illustrates a new classification proposal for hypnic headache, which will be included in the fourth chapter (Other Primary Headaches) of a new revision of the IHS classification (4). At present, some criteria – i.e., the intensity, duration and site of the pain – are still being debated and the most specific diagnostic criterion for the diagnosis of hypnic headache seems to be the occurrence of attacks exclusively during sleep. Compared with Goadsby and Lipton’s suggested criteria, the new proposal gives a longer attack duration (15-180 minutes), while the subcommittee underlines that there was disagreement over the features pain intensity and side (unilateral or bilateral).

Table IV (p. 216) summarises the main features of our eight patients, who do not entirely fulfil the diagnostic criteria proposed by Goadsby and Lipton (3).

The age at onset in our patients ranged from 50 to 83 years (average 58) and 6 of our patients were under 60. Literature data suggest that around a third of hypnic headache cases experience onset under the age of 60 (5-12). In the literature, age at onset of hypnic headache ranged from 30 to 84 years.

Six of our patients experienced ≥ 15 attacks/month, a high frequency that is in line with both literature data (91.8% of patients described experience more than 15 attacks/month) and the diagnostic criteria proposed in 1997 (3).

Two of our cases (patients 5 and 8) had an attack duration that fulfils the above-mentioned diagnostic criteria, in a further 2 duration could not be established due to the successful use of symptomatic treatment; while in the other 4 patients it was in excess of 60 minutes (ranging from 3 to 10 hours). In the literature, 45.9% of cases are reported to have a pain duration of over 60 minutes (5-8, 10,12-19), the longest being 9 hours. In the new classification the fact that the patient can present a duration longer than 180 minutes could be added as a comment.

The intensity of the pain was severe in 4 of our patients, moderate-severe in 3, and moderate in one. In the literature, 24.6% of cases report severe pain (5,7-10,12,15,17,20), 37.7% moderate pain (5,7,8,11,13,14,16), 8.2% moderate-severe pain (7,8,10,21) and 13.1% mild pain (1,5). Therefore severity of the pain does not appear to constitute a specific diagnostic criterion.

Five of our patients experienced unilateral pain, a finding that is at variance with Goadsby and Lipton’s criteria (3). However, a review of the literature data suggests that the pain is, indeed, unilateral in a sizeable proportion (36%) of subjects (5-10,12-15,22). Evers (personal communication, November 2002) in an analysis of literature cases including his own cases (no. = 65), found that 35% of patients have unilateral pain. Therefore, the site of pain does not seem to constitute a valid inclusion/exclusion criterion in hypnic headache.

In a small group (21.3%) of literature cases, slight associated symptoms (i.e., nausea, photophobia, phonophobia) are reported (1.5,8-11,13,16). Local autonomic symptoms (i.e., ipsilateral lacrimation/nasal congestion/palpebral ptosis) are reported in 6.6% of literature patients (5,8,9); similarly, 3 of our patients experienced associated symptoms (slight nausea) and none of our patients have presented local autonomic symptoms. In our opinion, mild general associated symptoms can accompany attacks, but oculocephalic autonomic symptoms should be excluded in order to avoid the possible overlapping or confusion with other primary headaches (i.e., cluster headache and other trigeminal-autonomic cephalalgias) that can occur during sleep.

The main characteristics of our patients, reveal, in accordance with the literature data, that attacks sometimes last longer than 180 minutes; that the intensity of the pain intensity is moderate-severe or severe in quite a large proportion of subjects; and that the pain is often unilateral.
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Gender (m/f)</th>
<th>Frequency (average/week)</th>
<th>Duration (m/w)</th>
<th>Pain Intensity</th>
<th>Location</th>
<th>Associated Symptoms</th>
<th>Autonomic Symptoms</th>
<th>Associated Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resnik 1988 (1)</td>
<td>6</td>
<td>5 M</td>
<td>67-70</td>
<td>1 F</td>
<td>7</td>
<td>30-60</td>
<td>mild</td>
<td>bilateral</td>
<td>nausea (3 pts)</td>
<td>none</td>
<td>lithium carbonate 100-400 mg</td>
</tr>
<tr>
<td>Newman 1990-91 (26)</td>
<td>4</td>
<td>3 F</td>
<td>86-94</td>
<td>1 F</td>
<td>7</td>
<td>15-60</td>
<td>--</td>
<td>bilateral</td>
<td>--</td>
<td>none</td>
<td>lithium carbonate 800 mg, propranolol, alprazolam (9 pts)</td>
</tr>
<tr>
<td>Gould 1991 (13)</td>
<td>1</td>
<td>1 F</td>
<td>65-65</td>
<td></td>
<td>7</td>
<td>120</td>
<td>moderate</td>
<td>unilateral</td>
<td>phonophobia, photophobia, nausea</td>
<td>none</td>
<td>lithium carbonate 480 mg</td>
</tr>
<tr>
<td>Quisling 1997 (11)</td>
<td>1</td>
<td>1 M</td>
<td>58-59</td>
<td></td>
<td>7</td>
<td>60</td>
<td>moderate-severe</td>
<td>bilateral</td>
<td>--</td>
<td>none</td>
<td>lithium carbonate 950 mg</td>
</tr>
<tr>
<td>Sibberdix 1997 (19)</td>
<td>6</td>
<td>1 F</td>
<td>60-78</td>
<td></td>
<td>7</td>
<td>20-120</td>
<td>moderate</td>
<td>bilateral</td>
<td>--</td>
<td>none</td>
<td>lithium carbonate 640 mg, caffeine (1 pt), dexamethasone (1 pt), propranolol (1 pt), diazepam (1 pt), serotonin antagonist (1 pt)</td>
</tr>
<tr>
<td>Dodick 1998 (9)</td>
<td>19</td>
<td>3 M</td>
<td>69-74</td>
<td>1 F</td>
<td>1-3 (6 pts) ≥ 4 (13 pts)</td>
<td>30-120</td>
<td>mild (1 pt)</td>
<td>bilateral</td>
<td>nausea (3 pts)</td>
<td>(1 pt)</td>
<td>(1 pt)</td>
</tr>
<tr>
<td>Matisse-Assan 1998 (14)</td>
<td>1</td>
<td>1 M</td>
<td>70-70</td>
<td>1 F</td>
<td>7</td>
<td>15-120</td>
<td>moderate</td>
<td>bilateral</td>
<td>(1 pt)</td>
<td>none</td>
<td>furazadine 5 mg (2 pts), lithium carbonate 420 mg (1 pt), lorazepam 3 mg (1 pt)</td>
</tr>
<tr>
<td>Ivnine 1999 (22)</td>
<td>1</td>
<td>1 M</td>
<td>74-74</td>
<td></td>
<td>7</td>
<td>30</td>
<td>--</td>
<td>unilateral</td>
<td>(2 pts)</td>
<td>none</td>
<td>lithium carbonate 480 mg, lorazepam 3 mg (1 pt)</td>
</tr>
<tr>
<td>Perez-Martinez 1999 (20)</td>
<td>1</td>
<td>1 F</td>
<td>69-69</td>
<td></td>
<td>2-3</td>
<td>15-45</td>
<td>severe</td>
<td>bilateral</td>
<td>--</td>
<td>none</td>
<td>lithium carbonate 950 mg</td>
</tr>
<tr>
<td>Klimik 1999 (3)</td>
<td>2</td>
<td>2 M</td>
<td>49-52</td>
<td>1 F</td>
<td>7 (1 pt)</td>
<td>120 (1 pt)</td>
<td>--</td>
<td>bilateral</td>
<td>none</td>
<td>(1 pt)</td>
<td>furazadine</td>
</tr>
<tr>
<td>Dodick 2000 (7)</td>
<td>3</td>
<td>2 M</td>
<td>48-69</td>
<td>1 F</td>
<td>7 (2 pts)</td>
<td>30-360</td>
<td>moderate</td>
<td>bilateral</td>
<td>(1 pt)</td>
<td>none</td>
<td>continuous positive airway pressure, dexamethasone (1 pt), sildenafil, indomethacin 75 mg (2 pts), melatonin 6 mg (1 pt)</td>
</tr>
<tr>
<td>Dodick 2000 (8)</td>
<td>7</td>
<td>2 M</td>
<td>46-71</td>
<td>1 F</td>
<td>1-2 (1 pt)</td>
<td>30-640</td>
<td>mild, moderate (1 pt)</td>
<td>bilateral</td>
<td>nausea (2 pts)</td>
<td>(1 pt)</td>
<td>indomethacin 75 mg, melatonin 6 mg (1 pt), sildenafil, indomethacin 75 mg (1 pt)</td>
</tr>
<tr>
<td>Argona 2000 (26)</td>
<td>1</td>
<td>1 F</td>
<td>79-79</td>
<td></td>
<td>7</td>
<td>30</td>
<td>--</td>
<td>bilateral</td>
<td>--</td>
<td>none</td>
<td>gabapentin 1200 mg</td>
</tr>
<tr>
<td>Lisetto 2000 (21)</td>
<td>1</td>
<td>1 F</td>
<td>79-79</td>
<td></td>
<td>30-40</td>
<td>moderate-severe</td>
<td>bilateral</td>
<td>none</td>
<td>none</td>
<td>lithium carbonate 650 mg</td>
<td></td>
</tr>
<tr>
<td>Cunha 2001 (9)</td>
<td>1</td>
<td>1 M</td>
<td>47-47</td>
<td></td>
<td>7</td>
<td>45-60</td>
<td>severe</td>
<td>unilateral</td>
<td>photophobia, paresthesias</td>
<td>indomethacin 150 mg</td>
<td></td>
</tr>
<tr>
<td>Martina 2001 (8)</td>
<td>1</td>
<td>1 F</td>
<td>68-68</td>
<td>3-7</td>
<td>40-120</td>
<td>moderate</td>
<td>bilateral</td>
<td>none</td>
<td>none</td>
<td>lithium 400 mg, tramadol 50 mg (3 pts), dextropropoxyphene (1 pt)</td>
<td></td>
</tr>
<tr>
<td>Cappello 2001 (19)</td>
<td>1</td>
<td>1 M</td>
<td>72-71</td>
<td>1 F</td>
<td>7</td>
<td>90</td>
<td>--</td>
<td>bilateral</td>
<td>none</td>
<td>none</td>
<td>pizotifen 15 mg, meclofenamate 3 mg</td>
</tr>
<tr>
<td>Rafia 2002 (17)</td>
<td>2</td>
<td>1 M</td>
<td>68-80</td>
<td>1 F</td>
<td>7</td>
<td>30-120</td>
<td>severe</td>
<td>bilateral</td>
<td>none</td>
<td>none</td>
<td>lithium carbonate 480 mg</td>
</tr>
<tr>
<td>Buonital 2002 (12)</td>
<td>1</td>
<td>1 F</td>
<td>60-60</td>
<td></td>
<td>7</td>
<td>some hours</td>
<td>severe</td>
<td>unilateral</td>
<td>none</td>
<td>none</td>
<td>lithium carbonate 150 mg</td>
</tr>
<tr>
<td>Viala-Dias 2002 (14)</td>
<td>4</td>
<td>1 M</td>
<td>49-66</td>
<td>3 F</td>
<td>7</td>
<td>60-120</td>
<td>moderate</td>
<td>bilateral</td>
<td>(1 pt)</td>
<td>(3 pts)</td>
<td>(1 pt)</td>
</tr>
</tbody>
</table>

* The patients also included in the cohort of Dodick's 1998 paper.
As regards the presence of concomitant diseases, we found two cases of arterial hypertension (therapeutically controlled), two cases of chronic obstructive lung disease without hypercapnia, and one case of snoring. Table V (see over) illustrates all the concomitant diseases that we found in the course of our review of the literature data on hypnic headache and also the concomitant pathologies observed in our hypnic headache patients. Of the literature patients, 13.1% presented arterial hypertension (5,9,14,17) and 6.6% respiratory sleep disturbances (5,7), two pathologies that can induce an early morning headache or a headache on awakening. In our opinion, an evaluation of arterial pressure parameters and respiratory function by means of 24-hour polysomnography would be important in future studies of patients suffering from hypnic headache syndrome in order to ascertain whether or not there is a significant association and to study their pathogenetic role in the syndrome. Therefore hypnic headache syndrome must be differentiated from the other primary headaches that can occur also in sleep, and from secondary nocturnal headaches (Table VI, over).

Cancer (of the bowel, prostate, lung or throat) was found in 8.2% of the literature cases; one of our cases, too, suffered from prostate cancer. However, both the long history of headache in these patients and the negative findings on radiological investigations of the head (CT scan or MRI) suggest that these are casual associations. The incidence of other pathologies associated with this syndrome is low, therefore suggesting that hypnic headache is a primary benign disorder generally appearing in later years.

As regards therapy, lithium salt (300-600 mg taken at bedtime) used to be considered the best therapeutic course in this disorder; but some patients were unresponsive or had only a transient partial response (5,18,23). In our patients, lithium was administered to patients 2 and 7 and produced a partial response in both of them, but also side effects in patient 7; it was also administered to patient 8, without success. A considerable proportion of the patients described in the literature discontinued lithium because of its side effects (5,18,24).

Indomethacin (50 mg) at bedtime prevented attacks in patient 5, but was ineffective in patient 8. In the literature, the administration of a daily dose of indomethacin

Table II - Diagnostic criteria for hypnic headache suggested by Goadsby and Lipton in 1997.

A. Headaches occur at least 15 times per month for at least one month.
B. Headaches awaken patient from sleep.
C. Attack duration of 5 - 60 min.
D. Pain is generalised or bilateral.
E. Pain not associated with autonomic features.
F. At least one of the following:
   1. There is no suggestion of one of the disorders listed in groups 5-11.
   2. Such a disorder is suggested but excluded by appropriate investigations.
   3. Such a disorder is present, but the first headache attack does not occur in close temporal relation to the disorder.

Table III - Proposal for hypnic headache diagnostic criteria, for inclusion in Chapter IV (Other Primary Headaches) of the second revised edition of the IHS classification.

4.5 Hypnic Headache

Previously used terms: hypnic headache syndrome, hypnic “alarm clock” headache syndrome

Description: attacks of dull pain that always occur after falling asleep.

Diagnostic criteria:

A. Headache has onset during and awakens patient from sleep, and does not occur at other times
B. Headache has all of the following characteristics:
   1. Occurs > 15 times per month
   2. Lasts at least 15 minutes after waking
   3. Onset after age 50
C. No autonomic symptoms and no more than one of the following:
   1. Nausea
   2. Photophobia
   3. Phonophobia
D. Not attributed to another disorder

Comment: the pain is usually mild-moderate, but severe pain is observed in approximately 20% of patients. Pain is commonly bilateral, but unilateral pain is reported in about one third of the cases. The attack usually lasts from 15 to 180 minutes, but pain longer than 180 minutes has been described in some cases. Caffeine or lithium have been reported to be effective treatments in several cases. Intracranial disorders or Trigeminal-Autonomic Cephalgias have to be excluded.
Table IV - Main features of our eight patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Onset (y)</th>
<th>Frequency (attacks/month)</th>
<th>Duration (min.)</th>
<th>Pain Intensity</th>
<th>Location</th>
<th>Associated symptoms</th>
<th>Autonomic symptoms</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>61</td>
<td>50</td>
<td>&gt; 15</td>
<td>15-20*</td>
<td>sev.</td>
<td>bilat.</td>
<td>nausea</td>
<td>none</td>
<td>melatonin 3 mg + caffeine 60 mg</td>
<td>reduction of intensity (after 3 months)</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61</td>
<td>52</td>
<td>15</td>
<td>180-360</td>
<td>mod./sev.</td>
<td>unilat. L.</td>
<td>none</td>
<td>none</td>
<td>lithium carbonate 450 mg</td>
<td>headache-free for 18 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>caffeine 60 mg</td>
<td>no change</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>61</td>
<td>54</td>
<td>&lt; 15</td>
<td>480-540</td>
<td>mod.</td>
<td>unilat. L.</td>
<td>none</td>
<td>none</td>
<td>gabapentin 800 mg</td>
<td>reduction of intensity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>melatonin 5 mg + caffeine 60 mg</td>
<td>reduction of intensity (after 12 months)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>55</td>
<td>52</td>
<td>15</td>
<td>60*</td>
<td>sev.</td>
<td>unilat. L.</td>
<td>none</td>
<td>none</td>
<td>no treatment</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>58</td>
<td>54</td>
<td>&gt; 15</td>
<td>60</td>
<td>mod./sev.</td>
<td>unilat. R.</td>
<td>none</td>
<td>none</td>
<td>dinitraine 30 mg + caffeine 75 mg</td>
<td>almost complete remission (after 12 months)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>69</td>
<td>67</td>
<td>&lt; 15</td>
<td>480-600</td>
<td>sev.</td>
<td>unilat. R.</td>
<td>none</td>
<td>none</td>
<td>caffeine 60 mg</td>
<td>no follow-up</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>84</td>
<td>83</td>
<td>&gt; 15</td>
<td>120</td>
<td>sev.</td>
<td>bilat.</td>
<td>nausea</td>
<td>none</td>
<td>lithium carbonate 450 mg</td>
<td>withdrawn (side effects)</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>67</td>
<td>52</td>
<td>&gt; 15</td>
<td>15-60</td>
<td>mod./sev.</td>
<td>bilat.</td>
<td>nausea</td>
<td>none</td>
<td>indomethacin 50 mg</td>
<td>no change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>prednisone 25 mg</td>
<td>no change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>caffeine 100 mg</td>
<td>reduction of intensity</td>
</tr>
</tbody>
</table>

* Attack duration with symptomatic treatment.
Caffeine (60-100 mg), alone or in association with melatonin (3-5 mg), was taken by 5 of our patients: two (patient 1 and patient 3) experienced a reduction of the pain intensity, one (patient 8) had a complete remission of the headache, another (patient 2) experienced no benefit, while the last patient (patient 6) has only just started the therapy. The literature contains no reports of melatonin taken in association with caffeine. A good response to caffeine (60 mg) – a cup of coffee in some patients (5) – has been reported and one patient experienced a remission with caffeinated soda associated with sustained-release indo-

Table V - Concomitant diseases in 61 cases of hypnic headache syndrome described in the literature and in our 8 cases.

<table>
<thead>
<tr>
<th>Concomitant diseases</th>
<th>Literature cases (no. = 61)</th>
<th>Present data (no. = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>8 (13.1%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Neoplasm (colon, prostate, lung, throat)</td>
<td>5 (8.2%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Respiratory sleep disturbance (snoring, sleep apnoea)</td>
<td>4 (6.6%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Hyperlipaemia</td>
<td>4 (6.6%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Degenerative alterations of the cervical spine</td>
<td>2 (3.3%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (3.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Generalised idiopathic epilepsy</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1 (1.6%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Heart arrhythmia</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Human immunodeficiency virus HIV-2 (serum positivity)</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Menière’s disease</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral meningioma</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophysis adenoma</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Prostate adenoma</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>0</td>
<td>2 (25%)</td>
</tr>
</tbody>
</table>

Table VI - Differential diagnosis of hypnic headache from other sleep headaches.

<table>
<thead>
<tr>
<th>Primary headaches</th>
<th>Secondary headaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trigeminal-autonomic cephalalgias</td>
<td>• Arterial hypertension</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>• Medication withdrawal</td>
</tr>
<tr>
<td>Paroxysmal hemicrania</td>
<td>(rebound headaches)</td>
</tr>
<tr>
<td>SUNCT syndrome (short-lasting unilateral neuralgiform headache with conjunctival injection and tearing)</td>
<td>• Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Migraine</td>
<td>• Increased intracranial pressure</td>
</tr>
</tbody>
</table>
methacin, 75 mg (8). In one patient, headache disappea-
red with 6 mg of melatonin (7) and in another with 3 mg of
melatonin associated with 1.5 mg of pizotifen (19). Cinna-
rizine (30 mg) associated with caffeine (75 mg) was seen to
produce an almost complete resolution of the heada-
che in our patient 5. In the literature, a good response to
other calcium antagonists has been reported in four pa-
tients (6,14). There was also one case of remission with
25 mg of atenolol (5) and another with cyclobenzaprine
(18).

Finally, two cases (17) experiencing a remission of head-
ache with prednisone are reported, but in one of our
patients this therapy was ineffective. In the literature,
one patient undertaking chemotherapy (prednisone +
cyclophosphamide + vincristine) for another condition
experienced a remission of hypnic headache (24).

One patient described in the literature experienced a
remission of attacks with 1200 mg of gabapentin (23);
in our patient 3, a lower dose of the same drug reduced
the intensity of the pain.

No drug has conclusively been found to have a specific
therapeutic efficacy on hypnic headache syndrome, but some (lithium, caffeine, melatonin) appear to play an
important role in its treatment. This could be reported
as a comment in the new IHS classification.

Our findings, together with data drawn from the literatu-
re, suggest that hypnic headache is characterised by a
variable clinical picture, as described for other primary
headaches – e.g., migraine (25) – and thus warrants a
variable therapeutic approach. Moreover, in the litera-
ture, hypnic headache occurs, in 21.3 % of cases
(1,5,7-9,13,16,19), in patients with a history of migraine
(i.e., migraine without aura in 11 patients, migraine with
aura in another 2). Two of our patients also had a hi-
story of migraine. Migraine history is frequently charac-
terised by a phenomenon called “phenotypical hetero-
cronia” (25), which consists of changes in the clinical
expression of the disease over time. The suggested in-
crease in the prevalence of migraine among patients
suffering from hypnic headache, as well as the observed
tendency of the latter to manifest itself at advanced ages, when migraine prevalence starts to sharply decli-
n (26), seems to suggest that hypnic headache and migraine may share a common neurobiological basis.

Therefore, it is tempting to hypothesise that the varia-
tion of external factors during or after the fifth decade of
life (changing hormonal levels associated with meno-
pause, reduction of work schedule upon retirement, and
others) may act on a common genetic predisposition re-
sulting in the expression of differentiated cranial pain
conditions. This finding may be explained as represen-
ting a predisposition to headache in these patients and
we recommend thorough investigation of their migraine
history since migraine prevalence seems to be higher in
hypnic headache subjects than in the general popula-
tion. Only new reports of hypnic headache syndromes
and standardised protocols for their diagnosis and treat-
ment will enable us to understand the pathophysio-
logy of this rare condition.

Acknowledgements

Our thanks go to Dr Cristina Tassorelli for her advice
during the preparation of this paper.

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