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Review Article

Hypnic headache: A review of 348 cases published from 1988 to 2018

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ABSTRACT

Hypnic headache (HH) is a rare benign disorder described initially by Raskin in 1988. It is characterized by recurrent nocturnal episodes of headache that periodically awaken the sleeping patient and usually occur in the elderly. This review aimed to describe the clinical features of the HH cases published in the literature from 1988 to 2018. Based on literature search in the major medical databases (LiLacs, SciELO, Bireme, Medline, Embase, Current Contents, Scopus, EBSCO and PubMed), we have analyzed the case reports on HH that have been published from 1988 to 2018. We described 343 adults (69.0% women and 31.0% men) and 5 children (3 girls and 2 boys) diagnosed with HH. Average age for adults and children was, respectively, 58.0 ± 13.1 years (ranging from 15 to 85 years) and 9 years (ranging from 7 to 11 years). The diagnosis was made 7.6 ± 14.2 years (range 0.1 to 39 years) after onset of headache. Pain occurred during nocturnal sleep (94.8%), with an average duration of 90 min, bilaterally located (55.5%), having a dull character (74.4%), and moderate intensity (61.5%). In 94.5% of the patients, headache occurred for 10 or more days per month (mean of 21 days). Autonomic manifestations occurred in 7.6% of the patients, predominantly lacrimation (61.1%) and rhinorrhea (16.7%). Caffeine presented the best therapeutic response in acute treatment. In prophylaxis, lithium, caffeine and indomethacin were effective drugs in 77.8% of the patients. In 56.7% of the patients there was remission with treatment and in 72.7% of them, without recurrence. HH is a rare disease that usually occurs for the first time in older women but may begin in childhood. Lithium and caffeine are effective drugs for pain prophylaxis, but randomized clinical trials are required.

1. Introduction

Hypnic headache (HH) is a rare headache syndrome first described by Raskin in 1988 [1]. It has also been called 'clockwise headache' or 'alarm-clock headache' [2]. It is characterized by recurrent nocturnal episodes of headache that periodically awaken the sleeping patient and usually occur in the elderly. Its pathogenesis is unknown [3,4].

This headache is a dull pain that develops only during sleep and awakens the patient. It occurs for 10 or more days per month, for more than three months and lasts > 15 min and for up to 4 h after waking up, predominantly in women after the age of 50. There are no autonomic symptoms or restlessness. The headache should not be attributed to another disorder [5,6].

Over the past 30 years, eleven large series of cases (≥10 patients per publication) have been published, totaling > 200 patients [5,7–16], and eight major reviews on HH [3,17–23]. According to these case series, HH was diagnosed in 0.07% to 0.1% of all headache patients assessed in headache centers, demonstrating the relative rarity of this condition [3].

In 2014, a major review of the 255 HH cases described since 1988 was published [23] based on case reports and eight major series [5,7–13]. In the last five years, almost a hundred new cases of HH have been described, but no other review was published.

This review summarizes the presently available information on clinical characteristics, pathophysiology and therapeutic options in HH patients reported from 1988 to 2018. Pediatric HH cases are discussed separately.

2. Patients and methods

Based on literature search in the major medical databases (LiLacs, SciELO, Bireme, Medline, Embase, Current Contents, Scopus, EBSCO and PubMed) we analyzed all reports or case series on HH that have been published from 1988 to 2018. We included all cases who were

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Table 1
Clinical and epidemiological characteristics of the 343 adult patients with hypnic headache analyzed in this review.

Characteristics	
Female/Male	69.0/31.0
Age of onset of pain (years)	58.0 ± 13.1 (15–85)
Latency until diagnosis (years)	7.6 ± 14.2 (0.1–39)
Timing of attacks	
Daytime naps	5.2
0:00–2:00 a.m.	27.6
2:00–4:00 a.m.	51.1
4:00–6:00 a.m.	16.1
Duration of attacks (minutes)	93.6 ± 65.3 (10–600)
< 30	3.4
30–120	78.0
> 120	18.6
Number of attacks per 24 h	1.3 ± 0.6 (1–6)
One	64.5
Two	29.7
≥Three	5.8
Frequency (days/month)	21.9 ± 7.6 (3 − 31)
< 10	5.5
≥10	94.5
Quality of pain	
Dull/pressure	74.4
Throbbing/Pulsatile	18.3
Stabbing/ Burning	7.3
Intensity of pain	
Mild (VRS 1–4)	5.5
Moderate (VRS 5–7)	61.5
Severe (VRS 8–9)	32.5
Very severe (VRS 10)	0.8
Localization of pain	
Unilateral (57.8% on the left; and 42.2% on the right)	30.3
Bilateral	55.5
Holocranial/difuse	14.2
Concomitant symptoms	
None	62.6
Nausea or vomiting (95.8% only nausea)	21.9
Photophobia or phonophobia	11.9
Photophobia and phonophobia	3.6
Trigemino-autonomic features	
Absent	92.4
Present (61.1% tearing; and 16.7% rhinorrhoea)	7.6

Note: Data are presented in percentages (%) and/or or arithmetic mean ± standard deviation (interval in parentheses). Data were not available from all patients for every aspect; VRS: verbal rating scale.

defined as having HH by authors and who fulfilled the diagnostic criteria of the ICHD-3 [6]. Demographic data, characteristics clinics and therapeutic experience were analyzed. Cases diagnosed as HH but secondary to other diseases were excluded from this study.

Data were analyzed based on demographic and clinical features, therapeutic experience and clinical outcomes. They are presented as arithmetic mean with standard derivation or as percentages. Percentage is always related to the total number of patients on whom information was available for the specific issue. All collected data were organized in database. The BioEstat version 5.0 for statistical analysis was used.

3. Results

A total of 348 published cases were analyzed for this review and fulfilled the selection criteria. There were 343 adults (69.0% women and 31.0% men) [1,4,5,7–10,12–16,24–83] and 5 children (three girls and two boys) [84–86] diagnosed with HH. Distribution of the 343 adult patients and their clinical and epidemiological characteristics are summarized in Tables 1 and 2, while the five pediatric cases are summarized in Table 3.

Table 2
Distribution of the 343 adults with hypnic headache from 1988 to 2018, according to age and sex.

Author(s), Year	Number of cases	Age or Average age (years)	Sex	
			Male	Female
Raskin, 1988 [1]	6	71.3	5	1
Newman et al., 1990 [24]	2	75.0	–	2
Goadsby and Lipton, 1997 [4]	1	84	–	1
Gould et al., 1997 [25]	1	65	–	1
Queiroz and Coral, 1997 [26]	1	59	1	–
Skobieranda et al., 1997 [27]	6	60–78	NR	NR
Dodick et al., 1998 [7]	19	60.5	3	16
Ivañez et al., 1998 [28]	1	74	1	–
Morales-Asín et al., 1998 [29]	3	75.3	1	2
Klimek and Sklodowski, 1999 [30]	2	50.5	2	–
Pérez-Martínez et al., 1999 [31]	1	70	–	1
Arjona et al., 2000 [32]	1	79	–	1
Dodick, 2000 [33]	3	57.7	2	1
Trucco et al., 2000 [34]	1	83	1	–
Zanchin et al., 2000 [35]	1	72	–	1
Centonze et al., 2001 [36]	1	47	1	–
Martins and Gouveia, 2001 [37]	1	68	–	1
Capo and Esposito, 2001 [38]	1	72	1	–
Vieira Dias and Esperança, 2002 [39]	4	57.0	1	3
Ghiotto et al., 2002 [40]	8	64.5	4	4
Pinto et al., 2002 [41]	8	58.5	1	7
Relja et al., 2002 [42]	2	74.0	1	1
Brooks et al., 2003 [43]	1	67	–	1
Evers et al., 2003 [44]	4	64.5	1	3
Pinessi et al., 2003 [45]	2	53.5	1	1
Sibon et al., 2003 [46]	1	68	–	1
Kocasoy Orhan et al., 2004 [47]	1	NR	–	1
Lisotto et al., 2004 [48]	4	71.2	1	3
Manni et al., 2004 [8]	10	67.9	4	6
Patsouros et al., 2004 [49]	1	60	–	1
Buzzi et al., 2005 [50]	1	70	–	1
Capuano et al., 2005 [51]	1	54	–	1
Domitrz, 2005 [52]	2	55.0	1	1
Dolso et al., 2006 [53]	1	40	1	–
Evans, 2006 [54]	1	56	–	1
Fukuhara et al., 2006 [55]	3	61.3	–	3
Guido and Specchio, 2006 [56]	1	67	–	1
Kerr et al., 2006 [57]	1	79	1	–
Peters et al., 2006 [58]	1	58	1	–
Porta-Etessam et al., 2006 [59]	8	NR	4	4
Schürks et al., 2006 [60]	1	71	–	1
Ulrich, 2006 [61]	1	78	–	1
Garza and Swanson, 2007 [62]	1	53	1	–
Marziniak et al., 2007 [63]	1	58	–	1
Antunno et al., 2008 [64]	1	63	–	1
Liang et al., 2008 [9]	17	69.6	9	8
Mitsikostas et al., 2008 [65]	1	68	1	–
Prakash and Dahbi, 2008 [66]	1	19	1	–
Seidel et al., 2008 [67]	1	54	–	1
Donnet and Lantéri-Minet, 2009 [10]	22	60.5	10	12
Porta-Etessam et al., 2009 [68]	1	36	1	–
Karlovasitou et al., 2009 [69]	1	54	–	1
Caminero et al., 2010 [70]	2	61.0	1	1
Holle et al., 2011 [71]	20	67.5	7	13
Bender, 2012 [72]	1	45	–	1
Dolezil and Mavrokordatos, 2012 [73]	1	64	–	1
Jiménez-Caballero et al., 2012 [13]	24	63–68	9	15
Mulero et al., 2012 [12]	13	56.7	2	11
Ouahmane et al., 2012 [74]	2	60.0	1	1
Son et al., 2012 [75]	1	64	–	1
Peng et al., 2013 [76]	2	55.5	1	1
Porta-Etessam et al., 2013 [77]	6	60.7	3	3

(continued on next page)

Table 2 (*continued*)

Author(s), Year	Number of cases	Age or Average age (years)	Sex	
			Male	Female
Silva-Néto and Almeida, 2014 [5]	25	72.5	5	20
Ruiz et al., 2015 [14]	23	56.2	4	19
Escudero Martínez et al., 2015 [15]	10	52.1	1	9
Arai, 2015 [78]	1	81	–	1
Aguirre-Rodríguez et al., 2016 [79]	1	46	NR	NR
Tariq et al., 2016 [16]	40	62.0	8	32
Fantini et al., 2016 [80]	1	49	–	1
Rehmann et al., 2017 [81]	1	74	–	1
Dissanayake et al., 2017 [82]	1	86	–	1
Pérez Hernández and Ontañón, 2017 [83]	1	41	–	1

Legend: NR - Not reported.

Table 3
Distribution of the 5 children with hypnic headache from 1988 to 2018, according to age and sex.

Author(s), Year	Number of cases	Age or Average age (years)	Sex	
			Male	Female
Grosberg et al., 2004 [84]	1	9	–	1
Scagni and Pagliero, 2008 [85]	1	8	–	1
Cerminara et al., 2011 [86]	3	9.3	2	1

3.1. Demographic data

The age of onset of headache in adult patients was 58.0 ± 13.1 years, ranging from 15 to 85 years. In only 9.0% of them, the onset of headache was before 50 years of age. The diagnosis was made 7.6 ± 14.2 years (range 0.1 to 39 years) after onset of headache. Based on chronological age in which the patient was treated and the time of pain until the diagnosis, it was possible to know the age of onset of pain.

It was not possible to calculate the prevalence of HH based on all published cases. However, in four large series of cases, the authors determined prevalence of 0.07% [7], 0.22% [5], 0.3% [9] and 1.1% [12]. As to geographic distribution, > 90% of the publications on HH occurred in seven countries: 99 cases in Spain; 80 in the USA; 40 in Italy; 35 in Brazil; 30 in Germany; 23 in France; and 17 in Taiwan [Fig. 1].

3.2. Clinical characteristics

Pain occurred during nocturnal sleep in 94.8% of the patients, with an average duration of 90 min (ranging from 10 to 600 min), distributed in the following percentages and times: 27.6%, before 2:00 a.m.; 51.1%, between 2:00 and 4:00 a.m.; and 16.1%, between 4:00 and 6:00 a.m. In 5.2% of the patients, pain occurred during daytime naps; in 0.6%, nightmares; and in 3.0%, vivid dreams.

In 94.5% of the patients, headache occurred for 10 or more days per month (mean of 21 days). The occurrence of a headache attack per night was observed in 64.5% of them, in a predictable time during sleep; two attacks, 29.7%; and three or more, in 5.8%.

The pain was bilateral in 55.5% of the cases; unilateral, in 30.3%; and holocranial or diffuse, in 14.2%. When the pain was unilateral, there was predominance of the left side (57.8%), typically in the frontotemporal region having a dull character in 74.4% of the patients; throbbing in 18.3%; and stabbing or burning in 7.3%. Pain intensity was mild in 5.5%; moderate in 61.5%; severe in 32.5%; and very severe in 0.8%. When the pain was considered of mild intensity, the patient managed to fall asleep again, despite the duration of the pain.

In 62.6% of the patients, no manifestation associated with headache was observed, but nausea or vomiting (21.9%), photophobia or phonophobia (11.9%), and photophobia and phonophobia (3.6%) occurred in 37.4% of them. Autonomic manifestations occurred in 7.6% of the patients, predominantly lacrimation (61.1%) and rhinorrhea (16.7%). These symptoms occurred mildly and bilaterally.

3.3. Therapeutic options

In assessing the therapeutic response, both acute and prophylactic treatment, only those drugs experienced in at least three patients are presented. Drugs efficacy was classified according to the statements of the respective authors [Tables 4 and 5].

Among the acute treatment options, caffeine, alone or associated with analgesics, was the most effective treatment, with a response rate higher than 70.0% [7,10,35,71,81]. It was recommended to ingestion of a cup of coffee, caffeine capsules or caffeine-containing analgesics.

Hypnotics and sedatives, despite a good response rate, were used in a few patients [4,62,78]. Thus, acetylsalicylic acid proved to be the second most useful option for acute treatment, with a response rate equal to 57.1% [44,63,76]. Other non-steroidal anti-inflammatory drugs were the most tested, but without efficacy [13,16,32,33,35,40,42,55,60,61,66,71,78,87].

Other drugs used in the treatment of migraine attacks, such as ergotamine and derivatives, dipyrone, acetaminophen and triptans were also tested, with response rates of 25.0%, 19.0% and 18.4%, respectively. The 100.0% oxygen inhalation was tested in nine patients [33,44,60,66,71,72], but treated the headache in only two of them [71,72], giving a response rate equal to 22.0%.

As for prophylactic treatment, several drugs that are commonly used in primary headaches, such as lithium, caffeine, indomethacin, calcium channel blockers, beta-adrenergic blockers, antidepressants (tricyclics and SSRIs), antiepileptics, serotonergic antagonists, melatonin and corticosteroids have been tested in prophylaxis of HH. However, only lithium, caffeine, indomethacin and melatonin were considered as effective options in preventive treatment in 77.8% (267/343) of the patients.

3.4. Follow-up

A sample of 97 patients with HH described in several case series, including three or more patients who also had a follow-up of more than five months was analyzed. Efficacy was classified according to the statements of the respective authors. In this sample, the follow-up periods of each patient were determined. In 56.7% of the patients there was remission with treatment and in 72.7% of them, without recurrence [Table 6].

3.5. Pediatric cases

From 1988 to 2018, only 5 children (three girls and two boys) were diagnosed with HH. The average age was 9.0 ± 1.6 years, ranging from 7 to 11 years. The diagnosis was made 15.8 ± 25.0 months (range 1 to 60 months) after onset of headache [84–86,88].

In all children, pain occurred during nighttime sleep lasting 10 to 30 min. Frequency of headache attacks ranged from one to three attacks per night, but in 80.0% of them, < 15 days of headache occurred in each month. The headache was mainly bilaterally located on the frontotemporal region having a throbbing character and moderate to severe intensity [84–86,88].

Most of the children (80.0%) did not take any medication during headache attacks because the pain was short-lived. Of the five children, one had spontaneous remission, two months after diagnosis [84]; in

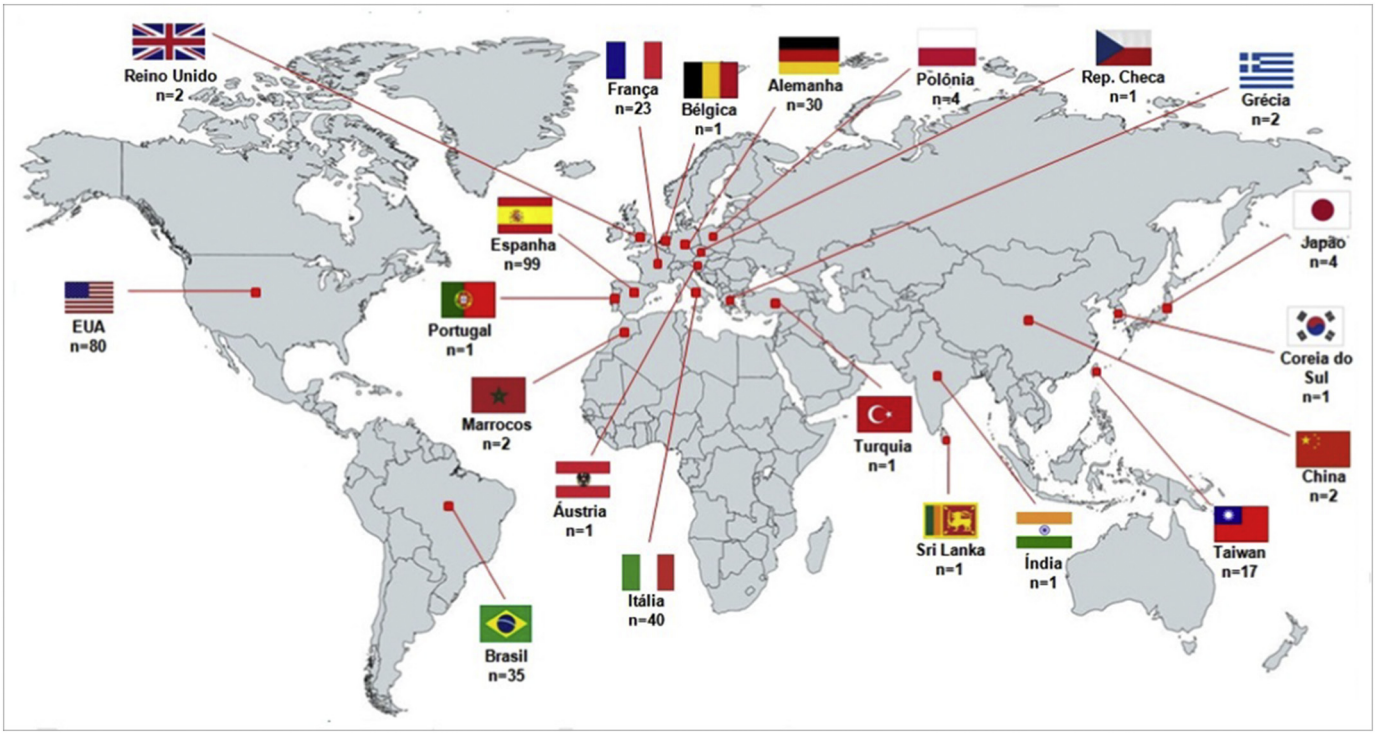

Fig. 1. Geographic distribution of 348 patients with hypnic headache (343 adults and 5 children), from 1988 to 2018.

Table 4
Acute treatment used for hypnic headache attacks.

Treatment[a]	n	Efficacy[b]			Response rate (A + B/n, %)
		None	Partial (A)	Good (B)	
Caffeine [7,10,35,36,41,71,81]	28	6	3	19	78.6
Caffeine-containing analgesics [10,41,54,63,71,87]	15	4	2	9	73.3
Acetylsalicylic acid [38,54,58,63,76,87]	7	3	3	1	57.1
Hypnotics and sedatives [4,62,78]	3	1	0	2	66.7
Ergotamine derivatives [33,36,38,60]	4	3	1	0	25.0
Opiates [60,71,81,82]	4	3	0	1	25.0
Oxygen inhalation [33,54,66,71,72,82]	9	7	0	2	22.2
Dipyrone or acetaminophen [14,16,55,61,71,74,79,80,82]	21	17	2	2	19.0
Triptans [13,16,33,54,56,60,63,66,71]	38	31	2	5	18.4
NSAIDs [13,14,16,32,33,35,40,55,60,61,66,71,78,87]	54	47	4	3	13.0

NSAIDs: nonsteroidal anti-inflammatory drugs.
[a] Only the treatments tested in at least three patients are presented.
[b] The efficacy is classified according to the statements of the respective authors.

two, headache attacks persisted for more than a year, but none used prophylaxis because of the low frequency of attacks [85,86]. Only two children were treated and used melatonin.

4. Discussion

HH is described in the literature as a rare headache syndrome, based on some studies which have shown its prevalence [5,7,9,12]. This low prevalence is confirmed by publication of only 348 cases over a period of 30 years. In addition, it is characterized by non-hereditary transmission and wide geographic distribution.

All 348 patients were diagnosed with HH prior to the current criteria. In ICHD-3 [6], pain is not required to occur after age 50, but this headache is extremely rare in young adults and children. For this reason, in this review, only 9.0% of adults and 5 children had this diagnosis.

The pain developed only during sleep, mainly nocturnal, causing the awakening in 100.0% of the sample, but in some patients, the headache appeared during naps or diurnal naps [7,9,15,40,41,45,53,66], according to Raskin's initial description in 1988 [1].

In the current classification, headache attacks should occur at ≥10 days per month for > 3 months, but in the sample studied, 5.5% of the patients presented < 10 days of headache per month, characterizing the episodic subtype. For this reason, some authors consider it as chronic or episodic headache, requiring further studies, in the long term, to define temporal patterns [90].

We found that in 100.0% of the cases, headache attacks lasted for > 15 min. Duration of pain was always a diagnostic criterion for hypnic headache. In the first cases described, the pain woke the patients and persisted for 30 to 60 min [1]. According to the first diagnostic criteria suggested, the duration of the headache attacks should be from 5 to 60 min [4]. Some years later, this duration changed from 10 to 180 min [3]. Finally, in the current diagnostic criteria, headache attacks last longer than 15 min and may last up to 4 h after waking up [6].

According to ICHD-3, for the diagnosis of hypnic headache, the absence of autonomic cranial symptoms or restlessness is necessary [6].

Table 5
Medications used in the prophylactic treatment of hypnic headache.

Treatment[a][b]	n	Efficacy			Response rate (A + B/n, %)
		None	Partial (A)	Good (B)	
Lithium [1,4,5,7,9,13,16,25–29,31–35,37–41,43,45,47–49,55,57,60,64,69–71,81,83]	128	34	9	85	73.4
Caffeine [7,8,13,16,38,40,44,48,55,60,61,63,71]	69	32	17	20	53.6
Indomethacin [7,12,13,15,16,25,28,32–36,38,40,43,46,50,56,58,60,61,66–68,70,71,73,77,78,81,82]	70	34	4	32	51.4
Melatonin [13,16,33,38,40,52,61,71,81]	26	13	2	11	50.0
Topiramate [12,13,16,64,71,81]	29	17	6	6	41.4
Flunarizine [9,12,13,29,30,38,41,44,45,52,56,59,64,77,81,82]	52	31	1	20	40.4
Beta-adrenergic blockers [1,7,16,18,26,32,38,40,41,45,56,66,89]	18	13	1	4	27.8
Tricyclic antidepressants [1,13,16,26,32,33,41,43,44,45,51,53,56,60,63,66,71,80,87]	49	38	2	9	22.4
Gabapentin [12,16,32,40,60,61]	9	4	1	4	55.5
Prednisone [7,33,35,40,42,60]	7	4	1	2	42.9
Verapamil [16,33,38,40,44,45,56,60]	11	8	0	3	27.3
Pizotifen [32,38,40,45,56]	5	4	0	1	20.0
SSRIs [4,16,25,32,33,43,66]	9	9	0	0	0.0
Lamotrigine [74,80]	3	0	0	3	100.0
Oxetorone [10]	8	0	8	0	100.0
Valproic acid /sodium divalproate [45,56,66,82]	5	5	0	0	0.0

SSRIs: selective serotonin reuptake inhibitors.
[a] Only the treatments tested in at least three patients are presented.
[b] The efficacy is classified according to the statements of the respective authors.

However, from the publication of reports or series of cases, it is observed that some patients present autonomic symptoms, but do not meet the full criteria for trigeminal-autonomic headaches [18], as was observed in 7.6% of our sample.

Attacks of HH are generally of moderate intensity and last less than two hours in > 80.0% of patients. Therefore, it is difficult to treat these headache attacks. Despite this difficulty, some drugs have been tested, although in few patients, and the results were not encouraging, but caffeine has shown good efficacy.

Prophylactic treatment provided better outcomes. According to the therapeutic response and the size of the sample that benefited from the treatment, possibility or probability of efficacy were expressed. Evaluation of this efficacy is shown in Table 7.

Lithium, caffeine, indomethacin and melatonin were first choice drugs and considered probably effective because they present the best response in pain control. Topiramate, lamotrigine, gabapentin and flunarizine were considered possibly effective drugs because they relieved pain, but in an unimpressive number of patients. Beta-adrenergic blockers, tricyclic antidepressants, SSRIs, verapamil, pizotifen, valproic acid and sodium valproate have been tested several times without any pain relief, so they are probably ineffective.

There are also other treatments tested in a single patient that have shown to be promising, requiring further studies, such as botulinum toxin, nerve stimulation and nerve block. In that case, they will be considered as future treatment options.

HH has unknown pathophysiology, but some hypotheses have already been suggested, such as chronobiological disorder, hypothalamic dysfunction or serotonin and melatonin dysregulation [18,91]. These hypotheses could explain the generation of pain and mechanism of action of some medications used in prophylaxis.

A chronobiological disorder has been hypothesized because many patients experience headache attacks at the same time in the night. Possibly, the suprachiasmatic nuclei are involved [17]. These nuclei are modulated by serotonin and have afferent and efferent projections for the periaquedutais gray and aminergic nuclei, which are important structures of the brainstem for modulation of pain [3,17,92].

Hypothalamic dysfunction hypothesis is based on the knowledge that the hypothalamus acts to control pain and sleep regulation because of its strong connections with periaqueductal gray matter, *locus coeruleus* and raphe nuclei [93]. In addition, the hypothalamus maintains connections to the caudal nucleus of the trigeminal tract through the trigeminal-hypothalamic tract [94].

There is decrease in the activity of the hypothalamic-pineal axis and suprachiasmatic nuclei with aging, causing a decrease in melatonin secretion [3,17,92]. On the other hand, lithium interferes in the metabolism of serotonin by increasing its release and deregulation of its receptors and, indirectly, increasing the level of melatonin [95,96]. Thus, lithium increases serotonergic neurotransmission in the

Table 6
Follow-up of patients with hypnic headache.

Authors	n	Remission without treatment	Remission with treatment		Without remission	Follow-up period (years)
			No recurrence	With recurrence		
	6	0	3	0	3	4.7 ± 2.9
Morales-Asín et al., 1998 [44]	3	0	2	1	0	1.1 ± 0.8
Dodick et al., 1998 [11]	17	1	4	0	12	3.6 ± 1.5
Pinto et al., 2002 [7]	8	0	1	0	7	ND
Ghiotto et al., 2002 [36]	7	0	0	1	6	ND
Evers et al., 2003 [20]	4	0	0	0	4	ND
Lisotto et al., 2004 [6]	4	0	1	3	0	2.5 ± 1.1
Fukuhara et al., 2006 [31]	3	0	3	0	0	ND
Liang et al., 2008 [54]	17	0	9	5	3	4.2 ± 2.3
Porta-Etessam et al., 2013 [66]	6	0	6	0	0	ND
Silva-Néto et al., 2014 [72]	22	0	11	5	6	≥ 0.5
Total (n, %)	97 (100.0)	1 (1.0)	40 (41.2)	15 (15.5)	41 (42.3)	

ND: Not available.

Table 7
Efficacy of pro phylactics of hypnic headache.

Probably effective (will happen)	Possibly effective (IT may happen)	Probably ineffective (will not happen)	New options
Lithium	Topiramate	Beta-adrenergic blockers	Botulinum toxin
Caffeine	Lamotrigine	Tricyclic antidepressants	Nerve stimulation
Indomethacin	Gabapentine	SSRIs	Nerve block
Melatonin	Flunarizine	Verapamil	
		Pizotifene	
		Valproic acid	
		Sodium valproate	

SSRIs: selective serotonin reuptake inhibitors.

hypothalamus [17,96] and this would explain its efficacy in the treatment of HH.

Regarding caffeine, there are different mechanisms in regulating pain. It acts by blocking the action of adenosine, making it a potent cerebral vasoconstrictor [97]. In addition, it interacts with adenosine receptors in peripheral sites, resulting in an anti-nociceptive effect [98].

5. Conclusions

Hypnic headache is a rare disease that usually occurs for the first time in older women but may begin in childhood. Lithium and caffeine are effective drugs for pain prophylaxis, but randomized clinical trials are required.

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Conflict of interest

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