

ARTIGO ORIGINAL/ORIGINAL ARTICLE

Broadening the Spectrum of Hypnic Headache: A Retrospective Cohort Study

Ampliando o Espectro da Cefaleia Hípnica: Um Estudo de Coorte Retrospectivo

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Abstract

Introduction: Hypnic headache is a rare headache disorder that requires strictly sleep-related attacks. There is also an ill-defined group of patients with recurrent predominant sleep-related nocturnal headache with occasional awake attacks, that are excluded from that diagnosis. Our aim was to compare these different groups and to understand whether their differences justify a distinct diagnosis.

Methods: This is a retrospective cohort comparative study of patients with predominantly nocturnal ($\geq 80\%$ attacks) recurrent headache (PNRH) and hypnic headache (HH) attending to a tertiary Headache Clinic.

Results: Thirty-one patients (83.9% female) were included, of whom 13 had PNRH, and 18 had HH (13 had probable and 5 definitive). There were no significant differences between groups regarding demographics, pain characteristics, and response to treatment. Both had a high (71%) frequency of previous migraine attacks and 51.7% fulfilled criteria for medication-overuse headache.

Conclusion: Our data suggests that there is an overlap between predominantly nocturnal headache and exclusively nocturnal hypnic headache. Moreover, both may evolve from migraine. Although the pathophysiology of these disorders remains unknown, recurrent nocturnal headache may be another probable form of hypnic headache.

Resumo

Introdução: A cefaleia hípnica é uma entidade rara que requer crises estritamente relacionados ao sono. Contudo, existem doentes com cefaleias noturnas recorrentes que apresentam ocasionais crises em vigília e que são excluídos desse diagnóstico.

O nosso objetivo foi comparar esses dois grupos de doentes e compreender se as suas diferenças justificam um diagnóstico distinto.

Métodos: Trata-se de um estudo de coorte retrospectivo, comparativo, entre doentes com cefaleia recorrente predominantemente noturna ($\geq 80\%$ das crises) (PNRH) e cefaleia hípnica (HH) seguidos numa clínica terciária de cefaleias.

Resultados: Foram incluídos 31 doentes (83,9% mulheres), dos quais 13 com PNRH e 18 HH (13 casos com HH provável e 5 HH definitiva). Não houve diferenças significativas entre os grupos quer na demografia quer nas características da dor e resposta ao tratamento. Ambos tinham uma frequência elevada (71%) de crises prévias de enxaqueca e 51,7% preenchiem os critérios para uso excessivo de medicamentos.

Conclusão: Estes resultados sugerem que existe uma sobreposição entre a cefaleia hipócnica e a cefaleia recorrente predominantemente noturna. Ambas podem evoluir a partir de enxaqueca. Embora a sua fisiopatologia permaneça desconhecida, a cefaleia noturna recorrente pode ser outra forma provável de cefaleia hipócnica.

Introduction

Hypnic headache (HH) is a rare primary headache disorder characterized by strictly sleep-related and nocturnal attacks. Any type of pain characteristics may fit this diagnosis, with exception of the typical trigemino-autonomic cephalalgias. HH is more common in women and typically initiates after the fifth decade of life.¹ However its exact prevalence remains unknown. Although it was first described in 1988 as a late-onset sleep-related headache syndrome,² the International Classification of Headache Disorders only recognized it as a primary headache in 2004 (ICDH-2).³ Following several attempts to characterize HH, the current criteria (ICDH-3,2018)⁴ remain strict in what concerns the timing of attacks that must occur exclusively during sleep and lead to awakening. However, if one of the other three defining features (minimum number of 10 episodes/month for >3 months, attack duration, and lack of autonomic features or restlessness) is missing, the diagnosis is of probable HH. Consequently, there is a group of patients with recurrent predominantly sleep-related nocturnal headaches who do not fulfil criteria for HH nor for other known condition, and whether this group represents variants of HH, or other distinct entities is still unclear.

The aim of this study was to describe and analyze a cohort of patients with nocturnal headache, including HH, probable HH and predominantly nocturnal recurrent headache (PNRH), and to compare them in terms of demographics, headache patterns and therapeutic response.

Material and Methods

Design and setting

Single center, retrospective cohort study of adult patients (> 18 years) presenting to an outpatient headache clinic in a tertiary hospital (Hospital Santa Maria, Lisbon-Portugal) between 2000 and 2020. Ethical approval was obtained from the Local Ethical Committee.

Patients and data collection

Patients were selected from the review of the medical records and data was collected from clinical records

and headache diaries. PNRH was defined as a sleep-related headache in which attacks occurred predominantly (>80%) during sleep, caused waking from sleep, and were not better accounted by another ICHD-3 diagnosis. We included patients with nocturnal headache who met ICDH-3 criteria for HH or probable HH and PNRH as defined above. Patients with cluster headache, other trigeminal-autonomic headaches, or secondary headaches were excluded. All patients were observed by a headache expert and secondary headaches were excluded by neuroimaging evaluation with computerized tomography or magnetic resonance imaging, and other exams whenever relevant (polysomnographic or blood pressure monitoring studies).

Patient characteristics including demographic information and clinical data (e.g., vascular risk factors, obstructive sleep apnea (OSA), nocturnal hypertension) were collected. Headache characteristics including age of onset, time of occurrence, frequency, duration, location, intensity, character, associated symptoms, acute pain medication and number of days of use, history, and clinical response to previous and current prophylactic drugs. We collected the number of different prophylactics tried and recorded good response to a prophylactic drug as a perceived 50% reduction in the number of monthly headaches. Previous history of migraine and change in previous pain patterns were also collected.

Statistical analysis

Data of continuous variables was tested for normality using the Kolmogorov-Smirnov test. Normal distribution continuous variables are presented as mean \pm standard deviation (SD) and non-normal continuous variables as median (interquartile range [IQR]). Categorical variables are expressed as frequency and percentage (n, %). Continuous variables were compared using independent samples t-test or Mann-Whitney U Test according to normality. Comparison between categorical variables was made using Fisher's exact test. All tests were performed to an alpha level of 0.05.

Results

Of all medical records reviewed, 31 patients met the study criteria, of whom 5 patients had HH, 13 had probable HH, and 13 fulfilled the criteria for PNRH. Patients were on their late 5th decade of life when headache began (57, IQR=52-64 years), the majority were female (n=26, 83.9%) of whom 65% (n=17) were postmenopausal women. A quarter (n=8, 25.8%) had a previous diagnosis of hypertension, a fifth (n=6, 19.4%) had depression at time of evaluation, and 16.1% (n=5) had OSA. Among patients who did not fulfill criteria for HH due to one criterion missing (including probable HH or PNRH), the criteria missing was the occurrence of a strictly nocturnal pain in 6 patients a minimum of 10 attacks per month in 3 patients and no restlessness or autonomic features in 8 patients. Patient demographics and headache characteristics are summarized in **Table 1**.

Patients had an average of 15 (IQR=9-30) days of headache per month. Regarding the timing of attack onset, in 12.9% (n=4) the pain awakened the patient between before 2AM, in 54.8% (n=17) between 2AM-4AM and in 32.2% (n=10) between 4AM-dawn. All patients reported moderate to severe pain, with a median duration of 45 (IQR=30-150) minutes. Concerning pain characteristics, 61.3% (n=19) of patients described the pain as throbbing/pulsating, 25.8% (n=8) as sharp/stabbing/burning and 12.9% (n=4) as dull. Almost half (n=15, 48.4%) had supraorbital/frontal pain and 22.6% had a diffuse pain. In 48.4% the pain was unilateral and in 45.2% bilateral. Migrainous features [nausea (46.2%), photophobia (30.8%) and cinesophobia (30.8%)] were present in 65% of patients, and 19.4% had trigeminal autonomic symptoms without criteria for any trigeminal-autonomic headache. Half of the patients reported hypermotor behavior during headache attacks. Although no significant differences were found between groups on any collected variables, there was a trend for headache attacks to occur mostly during dawn in the PNRH patients.

Almost 60% (n=18) of patients used first-line analgesics (paracetamol, non-steroid anti-inflammatory drugs or metamizole), one third recurred to triptans, and only three patients used opioids as rescue. At first consultation, patients had median of 24 (IQR=12.8-30) days of acute pain medication use per month. During follow-up, half (51.7%, n=15) of patients fulfilled crite-

ria for medication-overuse headache (MOH). Regarding prophylactic drugs, 58% (n=18) of patients tried one or two pharmacological classes, 22.6% (n=7) had three or four trials, and 19.4% (n=6) had tried more than five different drugs. Only 35.5% (n=11) had a good response to a prophylactic drug trial.

Over two-thirds of patients (70.1%, n=22) had previous history of migraine, and 20 (90.9%) of those were female. Most (54.5%, n=12) patients reported that pain characteristics changed over time (becoming more frequent, more severe, or featureless) and became predominantly nocturnal. In 31.8% (n=7), the usual migraine attacks resolved but a new ongoing nocturnal headache appeared, and in 13.6% (n=3) a nocturnal headache appeared in addition to the usual migraine.

Discussion

In our cohort of 31 patients with nocturnal headache only 5 patients met criteria for definite HH. These findings suggest that criteria may be strict, as other authors previously defended.^{5,6} Patients with de novo onset of PNRH did not fulfill criteria for any known headache disorder, which may pose diagnostic challenges for the diagnosis and therapeutic management. Pain occurred during nocturnal sleep between 2AM and dawn, and was of moderate to severe intensity, prompting a regular use of symptomatic treatment (mean 20 intakes/month) and fulfilling criteria for MOH in almost half of the cases. This occurred equally in PNRH and HH. Treatment delay to the following day, absence of a specific treatment, nocturnal awakening, and sleep cycle disturbance may determine more disability and greater impact in daily activities.^{1,7}

Previous studies reported a 36% prevalence of concurrent migraine or history of migraine in patients with HH,⁶ and in some HH patient's migraine stopped before HH attacks started.⁸ In our cohort, almost 65% of patients had migrainous features, and 71% reported history of migraine. Most of this subgroup of female patients got free of their usual migraine attacks or suffered a transformation of past migraine attacks into this new headache, losing its typical features in the post-menopause, becoming predominantly nocturnal. A recent study found that 39% of migraine patients had sleep-related migraine, defined as more than 75% of attacks during sleep and/or upon awakening.⁷ While it is typical of migraine to awake the patients in the early morning,

Table 1. Patient demographics and headache characteristics.

Characteristics	Total (n=31)	HH + pHH (n=18)	PNRH (n=13)	p-value
Age (y), median (IQR)	57.0 (12)	59 (15)	56 (8)	0.77
Sex, female, n (%)	26 (83.9)	14 (77.8)	12 (92.3)	0.285
Frequency (days/mon), median (IQR)	15 (21)	20 (19)	13 (19)	0.24
Timing of attacks, n (%)				0.29
Before 0h	3 (9.7)	3 (16.7)	-	
0h – 2h	1 (3.2)	1 (5.6)	-	
2h – 4h	17 (54.8)	8 (44.4)	9 (69.2)	
After 4h	10 (32.3)	6 (33.3)	4 (30.8)	
Duration (min), median (IQR)	45 (30-150)	45.0 (30-180)	42.5 (30-135)	0.63
Intensity of pain, n (%)				0.72
Mild	0 (0.0)	-	-	
Moderate	4 (12.9)	2 (11.1)	2 (15.4)	
Severe	27 (87.1)	16 (88.9)	11 (84.6)	
Character of pain, n (%)				0.77
Throbbing / pulsating	19 (61.3)	12 (66.7)	7 (53.8)	
Dull	4 (12.9)	-	2 (15.4)	
Sharp/ stabbing/ burning	8 (25.8)	-	4 (30.8)	
Side of headache, n (%)				0.81
Bilateral	14 (45.2)	8 (44.4)	7 (53.8)	
Unilateral	15 (48.4)	9 (50.0)	5 (38.5)	
Unilateral or bilateral	2 (6.5)	-	1 (7.7)	
Localisation, n (%)				0.94
Frontal	15 (48.4)	8 (44.4)	7 (53.8)	
Frontotemporal	5 (16.1)	3 (16.7)	2 (15.4)	
Frontoparietal	2 (6.5)	2 (11.1)	-	
Vertex	2 (6.5)	1 (5.6)	1 (7.1)	
Diffuse	7 (22.6)	4 (22.2)	3 (23.1)	
Migrainous features, n (%)	20 (64.5)	11 (61.1)	9 (69.2)	0.72
Trigeminal-autonomic features, n (%)	6 (19.4)	3 (16.7)	3 (23.1)	0.68
Motor activity, n (%)	17 (54.8)	10 (55.6)	7 (53.8)	0.60
Previous history of migraine, n (%)	22 (71.0)	14 (77.8)	8 (61.5)	0.43
Rescue medication, n (%)				
Simple analgesics (acetaminophen, NSAIDs, metamizol)	18 (58.1)	11 (61.1)	7 (53.8)	-
Combined analgesics	13 (41.9)	9 (50.0)	4 (30.8)	-
Ergotamine derivatives	14 (45.2)	10 (55.6)	4 (30.8)	-
Triptans	10 (32.3)	6 (33.3)	4 (30.8)	-
Opioid	3 (9.7)	3 (16.7)	-	-
Rescue medication (days/mon), median, (IQR)	24 (12.8-30)	20 (7.5-30)	23 (16-30)	0.661
Medication overuse headache, n (%)	15 (51.7)	8 (44.4)	7 (63.6)	0.71
Prophylactic medication, n (%)				
Lithium	11 (35.5)	6 (33.3)	5 (38.5)	-
Melatonin	6 (20.0)	4 (22.2)	2 (15.4)	-
Valproic acid	10 (32.3)	6 (33.3)	4 (30.8)	-
Topiramate	14 (45.2)	7 (38.9)	7 (53.8)	-
Flunarizine	8 (25.8)	5 (27.8)	3 (23.1)	-
Amitriptyline	8 (25.8)	3(16.7)	5 (38.5)	-
Treatment efficacy, n (%)	11 (35.5)	8 (44.4)	3 (32.1)	0.27
Prophylactic medication trials, n (%)				0.50
1 - 2	18 (58.0)	11 (61.1)	6 (46.2)	
3 - 4	7 (22.6)	3 (16.7)	4 (30.8)	
>4	6 (19.4)	3 (16.7)	4 (30.8)	

HH: hypnic headache, pHH: probable hypnic headache, PNRH: predominantly nocturnal recurrent headache, IQR: interquartile range, NSAIDs: non-steroid anti-inflammatory drugs

it is unusual to awake patients in pain in the middle of the night or dawn, as occurs in PNRH. Furthermore, it is recognized that age influences migraine prevalence, migraine features and also sleep. Migraine prevalence decreases with age and may lose its typical features in the elderly,⁹ and timing of pain onset changes over time (childhood migraine is worse in the afternoon after school activities,¹⁰ and in adults it becomes diurnal¹¹ or upon awakening). It is possible that in older adult's migraine attacks may shift towards dawn and become a nocturnal headache. Timing of pain attacks may be an increasingly relevant feature, and the association between migraine and HH deserves further investigation, as it can eventually broaden the spectrum of migraine drugs indications to include HH.

The retrospective study design does not allow conclusions on the associated diseases and medications neither on sleep characteristics, which were not always assessed with sleep studies. Additionally, a prospective analysis of caffeine intake, melatonin usage or indomethacin response in HH patients with trigeminal-autonomic features would be of benefit to help establish a more precise phenotype of PNRH patients. This is a pilot study and further studies with prospective longitudinal designs are needed.

Conclusion

Reducing the burden of headache disorders requires not only a better understanding of the factors affecting headache-related impact but also new insights into old entities. PNRH might be a variant of HH, which in some patients may evolve, late in life, from migraine. Given the large clinical overlap between the two conditions, namely the therapeutic response to the same group of agents (coffee and pharmacologic interventions), probable HH criteria could be changed to include PNRH (i.e., predominant (80%) nocturnal headache causing awakening, with ≥ 10 days/month for > 3 month, lasting from 15 minutes up to 4 hours and without cranial autonomic features). ■

Contributorship Statement / Declaração de Contribuição

IPM: Conceived and designed the study, participated in the discussion and critical revision of the manuscript and participated in the discussion and critical revision.

FS and MLR: Conceived and designed the study, acquired and analyzed the data and completed the first draft.

All authors have approved the version to be published.

IPM: Concebeu e desenhou o estudo, participou na discussão e revisão crítica do manuscrito e participou na discussão e revisão crítica.

FS e MLR: Conceberam e desenharam o estudo, adquiriram e analisaram os dados e completaram o primeiro rascunho.

Todos os autores aprovaram a versão a ser publicada.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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