

Brief Communications

Hypnic Headache Due to Hypoglycemia: A Case Report

Raimundo Pereira Silva-Néto, MD, PhD ; Adriana Almeida Soares, ND, MNutr;
Mário Fernando Prieto Peres, MD, PhD 

Hypnic headache (HH) is a rare primary headache disorder and pathophysiology is still poorly understood. It is considered a chronobiological disorder in almost all published cases. Few secondary cases have been described so far. We report a case of a 64-year-old woman presenting headaches exclusively during sleep and fulfilling the diagnostic criteria for HH, but a 72-hour glucose monitoring showed hypoglycemia episodes related to the onset of headaches. To our knowledge, this is the first report of symptomatic HHs associated with hypoglycemia and it suggests direct evidence of HH due to a metabolic disorder.

Key words: hypnic headache, nocturnal headache, sleep, hypoglycemia

(*Headache* 2019;59:1370-1373)

INTRODUCTION

Hypnic headache (HH) is a rare benign disorder described initially by Raskin in 1988.¹ According to current criteria, it is characterized by recurrent episodes of headaches that develop only during sleep, causing the awakening of the patient, and lasting for up to 4 hours, occurring on ≥ 10 days/month for > 3 months, without characteristic associated symptoms and not attributed to other pathology.²

The pathophysiology of HH is still unknown, but a dysfunction of the neural pathways of the brainstem that regulates the sleep–wake cycle in predisposed individuals is hypothesized.³ Although HH is regarded

as an idiopathic headache syndrome, several secondary cases have already been described.

To the best of our knowledge there are 13 reported cases of secondary HH due to posterior fossa meningioma,⁴ intracranial hypotension,⁵ ischemic stroke in the pontine reticular formation,⁶ angiotensin converting enzyme inhibitor withdrawal,⁷ nocturnal arterial hypertension,^{8,9} medication overuse,¹⁰ pituitary macroadenoma,¹¹ growth hormone-secreting pituitary tumor,¹² idiopathic cyclic edema,¹³ hemangioblastoma of the cerebellum,¹⁴ and arterial dolichoectasis.^{15,16}

We report a case of HH, in which the patient had hypoglycemia during sleep that was diagnosed by continuous glucose monitoring systems (CGMS) and responded to a specific targeted therapy. This clinical report was authorized for publication by the patient who completed a signed informed consent form.

CASE REPORT

We report a case of a 64-year-old right handed woman complaining of a 4-year history of daily

From the Department of Neurology, Federal University of Piauí, Teresina, Brazil (R.P. Silva-Néto); Center of Neurology and Headache of Piauí, Teresina, Brazil (A.A. Soares); Education and Research, Israelite Institute Albert Einstein, Teresina, Brazil (M.F.P. Peres).

Address all correspondence to R.P. Silva-Néto, Department of Neurology, Federal University of Piauí, Avenida Frei Serafim, 2280, Centro, Teresina, PI 64001-020, Brazil, email: neurocefaleia@terra.com.br.

Accepted for publication May 20, 2019.

Conflict Interest: None

Funding: None

headaches, lasting from 1 to 2 hours, awakening every night between 4 and 5 am. The headaches are located in the parietal bilateral and vertex region, intensity rated as 9 (0-10 scale) in weekly episodes with stronger headaches. However, most of the days would rate as 4. The pain was occasionally throbbing but most of the time dull, accompanied by mild phonophobia, vomiting, and photophobia. No autonomic symptoms have been reported in any of the headache attacks.

A food diary with a recollection of amount and time of meals and their supposed caloric count was evaluated. Her main meal was lunch. A light food intake occurred during breakfast and dinner. The last time she ate food was at 7 pm. This analysis disclosed a gap in time and amount of calories needed during the nocturnal period. The total calories needed were similar to the amount ingested. She went to bed regularly around 11 pm, taking 30 minutes to fall asleep, and awaking after a nocturnal headache around 8 to 9 am.

She would guess stress and some sleep problem could be possible causes but no clear trigger was identified. For pain relief ergotamines, triptans, and analgesic were prescribed without significant results. Previous preventive treatment trials failed including trazodone 150 mg, paroxetine 20 mg, and divalproex sodium 500 mg.

Her medical history included a gastroesophageal reflux disease treated with pantoprazole 40 mg, hypothyroidism treated with levothyroxine 50 mcg, both well controlled. She did not disclosed drinking or smoking habits. Although fatigue and daytime sleepiness were reported, snoring was absent.

Family history was positive for undiagnosed headaches on her mother, occurring during the day and not nocturnal. Her general medical and neurological examinations were unremarkable, blood pressure was 135/85 mm Hg on the initial visit, heart rate regular, 78 bpm, BMI 33.2, 160 cm, weight 85 kg.

MRI and MRA Angiogram of the brain were unremarkable, a polysomnography showed mild apnea, 7.8 episodes of apnea/hypopnea per hour, but no connection with the time of headaches appearing during the study of nocturnal sleep. Oxygen saturation was always higher than 90%.

A 24-hour blood pressure monitoring showed no significant rise during the period tested. A glucose 72-hour monitoring showed hypoglycemia episodes related to the onset of headaches (Fig. 1).

Her nocturnal headache attacks disappeared after re-scheduling her meal time and amounts by increasing the number of calories at night, on her regular 7 pm dinner and also advising her to take 100 to 200 calories before bedtime, through the ingestion of a cereal bar or yogurt. At the 12-month follow-up the patient was pain free.

DISCUSSION

In our patient, headache attacks always occurred during sleep for 4 years. Pain characteristics, such as age of onset, location, frequency, intensity, duration, time of occurrence, and absence of autonomic symptoms were typical of HH.

Whenever HH is suspected, even if the headaches fulfill the diagnostic criteria of ICHD-3 and the neuroimaging tests are normal, other possible causes

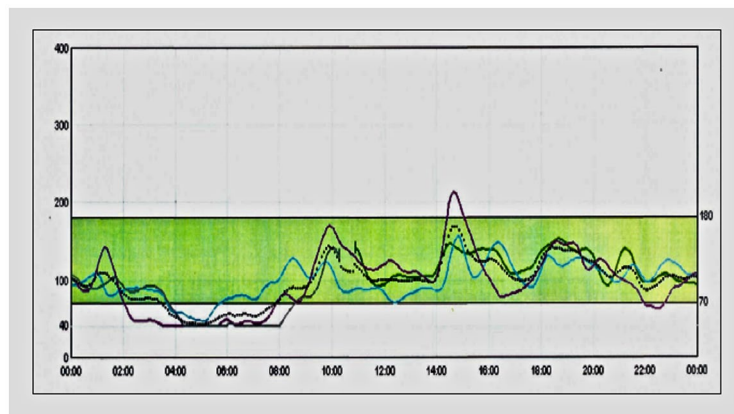


Fig. 1.—72-hour glucose monitoring in patient with nocturnal headache. [Color figure can be viewed at wileyonlinelibrary.com]

of nocturnal headache must first be ruled out, with special attention to sleep apnea/hypopnea syndrome, nocturnal hypertension, and medication overuse.¹⁷ We highlight the importance of considering hypoglycemia-induced headaches. Taking a careful look at the clinical history searching for gaps in the amount of calories ingested and also monitoring glucose levels were key for the diagnosis.⁸ This is a relative simple cause of headaches and yet an easy and effective treatment.

In the case described, a continuous blood glucose monitoring was performed for 72 hours. In about 80% of the time, glycemia ranged from 70 to 180 mg/dL, but in 19% of that time there was hypoglycemia between 3 and 6 am, while the patient was sleeping. During sleep, glycemia ranged from 40 to 92 mg/dL, with an average of 53 mg/dL. The disappearance of headache attacks after correction of nocturnal hypoglycemia points to a cause and effect relationship between hypoglycemia and HH.

Glucose monitoring is key in diabetes management advances in the field of glucose monitoring and has led to the development of non-invasive glucose monitoring, devices, and CGMS.¹⁸ This monitoring is a useful diagnostic tool for headache disorders with circadian variation where fluctuation of glucose levels are suspected as a trigger factor.

Although the pathophysiology of HH is still unknown, it is believed to be a chronobiological disorder because many patients experience headache attacks at the same time every night. This mechanism of biological pacemaker is exerted by the suprachiasmatic nucleus that is located in the anterior part of the hypothalamus. It has afferent and efferent projections to the brainstem structures for pain modulation.^{3,19}

There is great influence of the hypothalamus on HH due to its connections with periaqueductal gray matter, locus coeruleus, and raphe nuclei. In this way, it acts in the control of pain and the regulation of sleep.²⁰ In addition, the hypothalamus maintains connections with the caudal nucleus of the trigeminal tract through the trigemino-hypothalamic tract.²¹

Among the many reported cases of HH, some had type 2 diabetes mellitus as co-morbidity.^{8,17,22-26} However, in none of these patients was hypoglycemia responsible for the onset of pain. They became pain-free after HH treatment.

The concentration of serum glucose in the central nervous system (CNS) should be stable to meet energy

needs. During hypoglycemia, there is CNS activation in the attempt to maintain adequate levels of glucose, through gluconeogenesis in the liver.

Although hypoglycemia is a cause of secondary headache, the relationship between HH and hypoglycemia is not fully understood. We hypothesized that insufficient glucose supply in the suprachiasmatic nucleus and hypothalamus could trigger headache attacks in predisposed individuals. These structures have glucose as the main source of energy. Faced with hypoglycemia, they will be unable to function properly.

In addition, activation of the CNS by hypoglycemia triggers a variety of physiological events mediated by neural effects, such as altered cerebral blood flow and increased plasma norepinephrine release.²⁷ This mechanism has a connection with cerebral glycogen metabolism and its modulation by sympathetic activity, leading to an imbalance between the excitatory and inhibitory terminals, causing collective depolarization of the neurons.²⁸

CONCLUSIONS

To our knowledge, this is the first report of symptomatic HH associated with hypoglycemia and suggests direct evidence of HH due to a metabolic disorder.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Raimundo Pereira Silva-Néto, Adriana Almeida Soares, and Mário Fernando Prieto Peres

(b) Acquisition of Data

Mário Fernando Prieto Peres

(c) Analysis and Interpretation of Data

Raimundo Pereira Silva-Néto, Adriana Almeida Soares, and Mário Fernando Prieto Peres

Category 2

(a) Drafting the Manuscript

Raimundo Pereira Silva-Néto

(b) Revising It for Intellectual Content

Mário Fernando Prieto Peres

Category 3

(a) Final Approval of the Completed Manuscript

Raimundo Pereira Silva-Néto, Adriana Almeida Soares, and Mário Fernando Prieto Peres

REFERENCES

1. Raskin NH. The hypnic headache syndrome. *Headache*. 1988;28:534-536.
2. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
3. Evers S, Goadsby PJ. Hypnic headache: Clinical features, pathophysiology, and treatment. *Neurology*. 2003;60:905-909.
4. Peatfield RC, Mendoza ND. Posterior fossa meningioma presenting as hypnic headache. *Headache*. 2003;43:1007-1008.
5. Freeman WD, Brazis TW, Capobianco DJ, et al. Hypnic headache and intracranial hypotension. In: Proceedings of 46th Annual Scientific Meeting American Headache Society, 2004 June 10–13; Vancouver, British Columbia. *Headache*. 2004;44:498.
6. Moon H-S, Chung C-S, Hong S-B, Kim Y-B, Chung P-W. A case of symptomatic hypnic headache syndrome. *Cephalalgia*. 2006;26:81-83.
7. Eccles MJ, Gutowski NJ. Precipitation of long duration hypnic headaches after ACE inhibitor withdrawal. *J Neurol*. 2007;254:1597-1598.
8. Gil-Gouveia R, Goadsby PJ. Secondary “hypnic headache”. *J Neurol*. 2007;254:646-654.
9. Silva-Néto RP, Bernardino SN. Ambulatory blood pressure monitoring in patient with hypnic headache: A case study. *Headache*. 2013;53:1157-1158.
10. Baykan B, Ertas M. Hypnic headache associated with medication overuse: Case report. *Agri*. 2008;20:40-43.
11. Garza I, Oas KH. Symptomatic hypnic headache secondary to a non-functioning pituitary macroadenoma. *Headache*. 2009;49:470-472.
12. Valentini L, Tuniz F, Mucchiut M, et al. Hypnic headache secondary to a growth hormone-secreting pituitary tumour. *Cephalalgia*. 2008;29:82-84.
13. Godoy JM. Remission of hypnic headache associated with idiopathic cyclic edema with the use of aminophytone. *Open Neurol J*. 2010;4:90-91.
14. Mullally WJ, Hall KE. Hypnic headache secondary to haemangioblastoma of the cerebellum. *Cephalalgia*. 2010;30:887-889.
15. Moreira I, Mendonça T, Monteiro JP, Santos E. Hypnic headache and basilar artery dolichoectasia. *Neurologist*. 2015;20:106-107.
16. Fonseca M, Teotónio P, Fonseca AC. An unsuspected cause of hypnic-like headache. *J Neurol*. 2017;264:404-406.
17. Pérez Hernández A, Gómez Ontañón E. Influenza A virus: A possible trigger factor for hypnic headache? *Neurología*. 2017;32:67-68.
18. Vashist SK. Continuous glucose monitoring systems: A review. *Diagnostics (Basel)*. 2013;3:385-412.
19. Cohen AS, Kaube H. Rare nocturnal headaches. *Curr Opin Neurol*. 2004;17:295-299.
20. Montagna P. Hypothalamus, sleep and headaches. *Neurol Sci*. 2006;27:138-143.
21. Malick A, Strassman RM, Burstein R. Trigemino-hypothalamic and reticulohypothalamic tract neurons in the upper cervical spinal cord and caudal medulla of the rat. *J Neurophysiol*. 2000;84:2078-2112.
22. Centonze V, D’Amico D, Usai S, Causarano V, Bassi A, Bussone G. First Italian case of hypnic headache, with literature review and discussion of nosology. *Cephalalgia*. 2001;21:71-74.
23. Klimek A, Sklodowski P. Night headache. Report of 2 cases. *Neurol Neurochir Pol*. 1999;33:49-54.
24. Evers S, Rahmann A, Schwaag S, Lüdermann P, Husstedt IW. Hypnic headache – The first German cases including polysomnography. *Cephalalgia*. 2003;23:20-23.
25. Ouahmane Y, Mounach J, Satte A, Zerhouni A, Ouhabi H. Hypnic headache: Response to lamotrigine in two cases. *Cephalalgia*. 2012;32:645-648.
26. Arai M. A case of unilateral hypnic headache: Rapid response to ramelteon, a selective melatonin MT1/MT2 receptor agonist. *Headache*. 2015;55:1010-1011.
27. Hufnagl KN, Peroutka SJ. Glucose regulation in headache: Implications for dietary management. *Expert Rev Neurother*. 2002;2:311-317.
28. Dalkara T, Kiliç K. How does fasting trigger migraine? A hypothesis. *Curr Pain Headache Rep*. 2013;17:368.