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CLINICAL CORRESPONDENCE

Hypnic headache secondary to a growth hormone-secreting pituitary tumour

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Hypnic headache (HH) is a rare, benign, chronic headache disorder, usually affecting aged people and characterized by a close relation to sleep. It was first described by Raskin in 1988 (1). Diagnostic criteria for HH have been established, and HH is included in the recent International Headache Society (IHS) classification as a primary form of headache (IHS classification 4.5) (2).

At the time of writing, >100 cases have been reported in the literature (for review see (3)). Furthermore, several patients with this disorder have been described in Italy (4–12). The pathophysiology of HH remains unclear (13). In most instances, even extensive neurological and neuroradiological examinations will be normal (14). However, symptomatic HH has been reported in relation to obstructive sleep apnoea syndrome (15), arterial hypertension (3), pontine stroke (16) and posterior fossa meningioma (17). We report a case of HH in an acromegalic patient with an intrasellar pituitary adenoma.

Case report

A 66-year-old man presented to his primary-care doctor with a 9-month history of paraesthesias in both hands. On examination, he had features of acromegaly including broad hands and feet, hypertrophy of the mandible and macroglossia. His body mass index was 28.1. On direct questioning, the patient admitted to fatigue, arthralgias and myalgias over the preceding 3 years and reported a 10-kg weight gain in the last 4 years despite diet and exercise. He had also noticed that his wedding ring had become tight on his finger. The patient was referred to an endocrinologist for further evaluation and management. His random growth hormone (GH) levels were 6.6 ng/ml (normal range < 5 ng/ml), his insulin-like growth factor 1 (IGF1) was elevated to 525 ng/ml (reference range 55–258 ng/ml), and a subsequent oral glucose tolerance test confirmed active acromegaly (serum GH nadir > 1 ng/ml). The other neuroendocrine test results were normal, as well as a routine neuro-ophthalmological examination. A specific magnetic resonance imaging (MRI) scan of the sellar region revealed a 7-mm mass in the left anterior pituitary gland, suggestive of a microadenoma. The patient was offered trans-sphenoidal surgery as primary therapy given the small size of the lesion, the lack of invasion into the cavernous sinus and the excellent cure rate at the centre where he was seen (18). When he was admitted to the Department of Neurosurgery, he reported a 1-year history of strictly nocturnal headache attacks, so he underwent neurological evaluation.

The patient had approximately 20 headaches a month that had gradually increased from an initial frequency of 7–8 headaches a month. The headaches awakened him after 2–3 h of sleep (bedtime 23.00 h) and lasted from 20 to 40 min. He could not describe an exact relationship with the dreams. The pain was located bilaterally over the frontal region; it was throbbing in quality and of moderate intensity (6/10 on a visual analogue scale from 0 to 10). The patient denied nausea, vomiting, photophobia, phonophobia, or any autonomic symptoms such as ptosis, lacrimation, rhinorrhoea, nasal obstruction, or reddening of the eye. During the attacks, he got out of bed, calmly waiting for the pain to subside. The pain decreased spontaneously without medication. After the headache resolved, he was usually able to fall asleep again. He had no headaches during the day. His medical history was remarkable

for essential hypertension, which was well controlled by atenolol 50 mg plus ramipril 2.5 mg/day. Suspecting that the nocturnal headaches could be caused by high blood pressure, he often measured his blood pressure during the headache attacks, but the values remained in his usual range (130/80 mmHg). He had a remote history of migraine without aura. His mother and son both had migraine headaches. He did not smoke or drink alcohol regularly and had no allergies. Neurological examination was normal. Unfortunately, the patient refused to have a polysomnography. He underwent total resection of the pituitary tumour via trans-sphenoidal approach. As expected, the tumour was microscopically a benign GH-secreting micro-adenoma. The patient's postoperative course was uncomplicated. The diurnal excretion of GH returned to normal, and the patient had normal GH release after oral glucose loading. The level of IGF1 also returned to normal. An MRI 4 months after treatment and again at 12 months after treatment both showed no evidence of residual adenoma. The patient's acromegalic features improved over the follow-up period of > 1 year. Most importantly, the patient has been absolutely free from further headache attacks after the removal of the tumour.

Discussion

We report the case of a 66-year-old man with a GH-secreting pituitary tumour who experienced a headache fulfilling 2004 IHS diagnostic criteria for HH. The complete cessation of headache attacks after trans-sphenoidal surgery reasonably points to a cause and effect relationship between the GH-secreting tumour and the HH.

The pathophysiology of HH is still unknown (13). The strict association with sleep, the onset at a consistent time each night and the efficacy of drugs that can impact circadian rhythms, such as lithium and melatonin, strongly suggest that pain onset may be controlled by a time-related mechanism, possibly located in the suprachiasmatic nucleus (SCN), the hypothalamic area considered to be the human biological clock (1, 13, 19, 20). The SCN projects to and receives afferents from the brainstem periaqueductal grey, so a functional link to the pain-modulating system is feasible (13).

The pathophysiology of pituitary-associated headache is poorly understood too (21). A recent study in patients with pituitary tumours has suggested that headache may be a biochemical–neuroendocrine problem rather than a structural one (22). A variety of headache phenotypes have been associated with pituitary tumours. These include chronic and episodic migraine, cluster headache and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (23). To our knowledge, there are no previously reported patients who have suffered from an intrasellar tumour and concomitant HH. Given the anatomical contiguity between the pituitary gland and the SCN, a plausible explanation for our patient's HH would be that local pressure effects have altered the relationships between SCN and brainstem periaqueductal grey. However, the small size of the lesion argues against this explanation. Therefore, a role for the biochemical–neuroendocrine abnormalities in the aetiology of pituitary-associated HH may be hypothesized. In this regard, it would have been desirable to assess formally the endocrine treatment responsiveness in this patient.

In conclusion, this case can be added to the sample of patients with secondary HH reported to date in the literature. Furthermore, it emphasizes that a cranial MRI remains essential for proper evaluation of patients that present with nocturnal headache attacks.

References

1 Raskin NH. The hypnic headache syndrome. Headache 1988; 28:534–6.
2 Headache Classification Committee of the International Headache Society. Classification and diagnosis criteria for headache disorders, cranial neuralgias, and facial pain, 2nd edition. Cephalalgia 2004; 24 (Suppl. 1):1–160.
3 Gil-Gouveia R, Goadsby PJ. Secondary 'hypnic headache'. J Neurol 2007; 254:646–54.
4 Zanchin G, Lisotto C, Maggioni F. The hypnic headache syndrome: the first description of an Italian case. J Headache Pain 2000; 1:60.
5 Trucco M, Maggioni F, Badino R, Zanchin G. Hypnic headache syndrome: report of a new Italian case. Cephalalgia 2000; 20:312.
6 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; 21:71–4.
7 Relja G, Zorzon M, Locatelli L, Carraro N, Antonello RM, Cazzato G. Hypnic headache: rapid and long-lasting response to prednisone in two new cases. Cephalalgia 2002; 22:157–9.
8 Ghiotto N, Sances G, Di Lorenzo G, Trucco M, Loi M, Sandrini G et al. Report of eight new cases of hypnic headache and mini-review of the literature. Funct Neurol 2002; 17:211–19.
9 Pinessi L, Rainero I, Cicolin A, Zibetti M, Gentile S, Mutani R. Hypnic headache syndrome: association of the attacks with REM sleep. Cephalalgia 2003; 23:150–4.

10 Lisotto C, Mainardi F, Maggioni F, Zanchin G. Episodic hypnic headache? Cephalalgia 2004; 24:681–5.
11 Manni R, Sances G, Terzaghi M, Ghiotto N, Nappi G. Hypnic headache: PSG evidence of both REM- and NREM-related attacks. Neurology 2004; 62:1411–13.
12 Capuano A, Vollono C, Rubino M, Mei D, Cali C, De Angelis A et al. Hypnic headache: actigraphic and polysomnographic study of a case. Cephalalgia 2005; 25:466–9.
13 Evers S, Goadsby PJ. Hypnic headache: clinical features, pathophysiology, and treatment. Neurology 2003; 60:905–9.
14 Evers S, Rahmann A, Schwaag S, Lüdemann P, Husstedt IW. Hypnic headache—the first German cases including polysomnography. Cephalalgia 2003; 23:20–3.
15 Dodick DW. Polysomnography in hypnic headache syndrome. Headache 2000; 40:748–52.
16 Moon HS, Chung CS, Hong SB, Kim YB, Chung PW. A case of symptomatic hypnic headache syndrome. Cephalalgia 2006; 26:81–3.
17 Peatfield RC, Mendoza ND. Posterior fossa meningioma presenting as hypnic headache. Headache 2003; 43:1007–8.
18 Clemmons DR, Chihara K, Freda PU, Ho KK, Klibanski A, Melmed S et al. Optimizing control of acromegaly: integrating a growth hormone receptor antagonist into the treatment algorithm. J Clin Endocrinol Metab 2003; 88:4759–67.
19 Dodick DW, Mosek AC, Campbell JK. The hypnic ('alarm clock') headache syndrome. Cephalalgia 1998; 18:152–6.
20 De Simone R, Marano E, Ranieri A, Bonavita V. Hypnic headache: an update. Neurol Sci 2006; 27 (Suppl. 2):144–8.
21 Abe T, Matsumoto K, Kuwazawa J, Toyoda I, Sasaki K. Headache associated with pituitary adenomas. Headache 1998; 38:782–6.
22 Levy MJ, Jager HR, Powell M, Matharu MS, Meeran K, Goadsby PJ. Pituitary volume and headache: size is not everything. Arch Neurol 2004; 61:721–5.
23 Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. Brain 2005; 128:1921–30.