BRIEF REPORT

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A case of a GH-producing pituitary adenoma associated with a unilateral headache with autonomic signs

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Abstract A 66-year-old man suffered from a drug-resistant, left-sided headache with autonomic signs, triggered by the supine position. The acromegalic facies initially suggested a possible increase in basal plasma levels of GH, but routine haematological controls excluded abnormal values of GH. Cerebral and facial CT scan and MRI did not detect any alterations in the nasal sinuses, except for a mucous cyst. Surgical ablation of the cyst did not alleviate the pain. Further endocrinological tests demonstrated an increase of IGF-1 (somatomedin C), and another MRI scan of the sellar region confirmed the presence of a pituitary macroadenoma on the left paramedian side. After an initial improvement of the symptomatology due to trans-sphenoidal ablation of a benign GH-producing macroadenoma, the headache worsened again. Pain was well correlated with the increased plasma levels of IGF-1. The patient died suddenly for myocardial infarct.

Key words Headache • GH-producing pituitary adenoma • Somatomedin C (IGF-1)

Introduction

Ten to fifteen percent of all diagnosed cerebral tumours are pituitary adenomas (60%–70% are secreting adenomas) that frequently occur during the 3rd or 4th decades of life. Half of them are diagnosed early by clinical hormonal symptoms even when the dimensions of the adenomas are small (5 mm) and the tumours are undetected on magnetic resonance imaging (MRI) scans. Among these, however, growth hormone (GH)-producing macroadenomas are uncommon, and often have blood hormonal levels so low that their diagnosis could be delayed [1, 2]. In 10% of the adult population, MRI scans can detect silent pituitary adenomas [3].

Thirty-three to seventy-two percent of pituitary adenomas, independently of their dimensions, induce headache [4, 5]. Headache is the first symptom in about 11% of women and in about 15% of men [6]. Some studies have suggested that the incidence of headache was 57.1% in non-functioning adenomas [7] and 60% in GH-secreting adenomas [8]. Headache seems to be more frequent in prolactin (PRL)-secreting adenomas (57.1%) than in GH-secreting adenomas (12.5%) [9]. Headache, more frequently localised to the frontal region, is bilateral (89.5%) or monolateral (84.2%) and sometimes diffuse (42.1%). Pain is continuous or pressing-heavy, and rarely pulsating-intermittent (mostly in female patients) (57.9%) [9].

Headaches due to GH-secreting adenomas, with or without acromegaly, do not have significant sellar abnormalities or visual problems [5, 8].

Case history

A 56-year-old patient, without familiarity of headache, suffered from headache for the last 20 years of his life. He was referred to our headache centre where he was treated for 10 years until he died. From the beginning, the almost daily headache had a pressing quality, was localised on the left temporal side, and lasted 7–8 h. Pain was usually diffuse to the ipsilateral orbito-frontal and/or maxillary regions, associated with bilateral blurred vision, lacrimation, conjunctival injection and rhinorrhoea (only on the left side), but not with nausea or vomiting. Physical activity did not modify the pain. The headache usually started during the evening. The sleeping position exacerbated the associated autonomic symptoms; instead, the orthostatic position and/or walking alleviated the pain. In fact, the patient frequently stood up during the night.

Over time, the headache worsened in intensity and frequency: attacks became continuous and intolerable, without relief during the day or after pharmacological treatment.

In 1992, the patient was referred to our headache centre with a diagnosis (formulated in 1988) of "antero-septal coronary infarct, double coronary artery by-pass surgery, diabetes mellitus, and unspecified paroxysmal headache". During the initial diagnostic work-up at our headache centre, the patient underwent an otological visit that evidenced hypertrophy of the inferior turbinates and right deviation of the nasal septum. This alteration suggested the diagnosis of "Headache associated with a disorder of nose and sinuses" according to the International Classification of Headache Disorders (ICHD)-II [10].

Five years later, a follow-up visit revealed the presence of acromegalic facies; however, plasma GH levels were normal. In the same year, the patient underwent a computed tomography (CT) scan of the nasal sinuses that showed the presence of a mucous cyst (2.5 cm in diameter) in the alveolar recess of the left maxillary sinus. The cyst was surgically removed one month after the instrumental diagnosis, but with no modification of the headache.

A cluster-like headache (CLH) was suspected for the possible involvement of trigeminal fibres stimulated by abnormalities of the nasal sinus, as suggested by the otological visit. The cardiovascular parameters of the patient, strictly monitored by the cardiologist, were normal, thus allowing administration of sumatriptan and oxygen, with only slight improvement of the pain. Also, verapamil (360 mg/day) and prednisone (50 mg/day) prophylaxis, as well as instillation of Bonheim solution (cocaine 1/3, phenol 1/3 and menthol 1/3) on the sphenopalatine ganglion were ineffective.

In October 2000, an MRI scan of the brain and paranasal sinuses showed a small, 5–7 mm diameter focal area in the right cerebellar hemisphere that was identified as a capillary telangiectasia. A subsequent cerebral MRI scan (February 2001) revealed a small ischaemic lesion of the right frontal region, probably related to severe stenosis of the right internal carotid artery. The patient subsequently underwent carotid endarterectomy.

Headache persisted for six months and a routine control of haematological parameters revealed an increase in the erythrocyte sedimentation rate (ESR) of 44 mm (normal: 2–15 mm), and C-reactive protein (CRP) of 240 mg/dl (normal: <80). The high values of ESR and CRP, the patient's age, and the spontaneous and/or evoked pain on the left temporal side suggested a probable Horton's arteritis. This hypothesis was not confirmed by histological examination, which showed chronic inflammation of the external layer without typical multinuclear giant cells.

In May 2001, a new endocrinologic screening test revealed an increase in IGF-1 (somatomedin C) (665 ng/ml; normal range: 44–279 ng/ml). Two months later, the patient underwent a specific MRI scan of the sellar region, which revealed a pituitary macroadenoma (12 mm diameter) on the left paramedian side. This lesion reached the left side of the cavernous sinus without infiltration of the sinus wall. The optic chiasm was not involved. In October 2001, the pituitary macroadenoma was removed by trans-sphenoidal procedure. The histological examination revealed a benign GH-secreting macroadenoma.

Three months after surgery, the headache significantly improved without any prophylactic therapy; the pain disappeared during the day and was greatly reduced during the night. Only a mild, left frontal-temporal pressing headache persisted and nocturnal rest improved. Other clinical features persisted: evoked pain in the left temporal region, moderate increase of arterial blood pressure (150/90 mmHg) and ventricular concentric hypertrophy.

In February 2002, a further cerebral and facial MRI with contrast enhancement revealed a hypodense area of the left paramedian side of the sella turcica. This area was considered a result of previous surgery or a residual of the tumour. The contemporary IGF-1 levels showed a 35% reduction compared to previous levels (402.2 ng/ml). Although neuroradiological examination failed to confirm involvement of the optic chiasm, visual field testing revealed the presence of a partial, bitemporal hemianopsia, more evident on the left side.

One month later, in March 2002, during a subsequent medical control, the patient referred a new, mild worsening of the headache. Nocturnal hyposensitivity and

paraesthesia of the arms, previously alleviated during movement, worsened again. The persisting high levels of IGF-1 (444.4 ng/ml), acromegalic-like symptoms and the last neuroradiological report suggested the hypothesis of a residual GH-secreting adenoma located behind the left carotid sinus.

The patient was re-evaluated by the neurosurgeon and endocrinologist, and both specialists decided to begin inhibitor therapy with octreotide before attempting another surgical approach. In June 2002, in spite of specific therapy, the levels of IGF-1 increased to 473.5 ng/ml, without any improvement in the symptomatology. In July 2002, the patient died suddenly, probably from relapse of a myocardial infarction. An autopsy was not performed for legal reasons.

Discussion

GH-producing macroadenomas are uncommon secreting adenomas, often with a delayed diagnosis, especially due to poor laboratory diagnostic support [6].

Several authors report CLH related to facial and cavernous sinus diseases [11]. The mechanisms underlying these symptoms are the object of discussion. Hannerz [12] hypothesised that the adenoma induced an impairment of venous flow in the carotid sinus and/or of the superior ophthalmic vein with subsequent vasculitis of the orbital sinus. These events caused stimulation of the first or second trigeminal branches and activation of the trigeminovascular system [12–15]. Other authors hypothesised, instead, that the adenoma pulled on the bony sellar septum and excited the meningeal arteries and trigeminal fibres located there [4, 16].

In the case of CLH, inflammation of the sphenoidal sinus due to aspergilloma was reported by Zanchin [15], while inflammation of other nasal sinuses was suggested by Takeshima [17] and Molins [18]. CLH was referred to be secondary to the subclavian steal phenomenon [19], and recently a case of migraine with aura was reported that resolved after treatment of a PRL-secreting pituitary microadenoma [20].

In our case, a differential diagnosis between maxillary sinus infection and sphenoidal sinusitis was made. Also considered was the diagnosis of Horton's arteritis because of the age of the patient, the increase in ESR and CRP, and the site and pattern of pain. The patient's headache did not fulfil ICHD-II criteria for CLH; in fact, crises so prolonged and pain so progressive and exacerbated by the supine position are suggestive of a secondary form of headache. Another possible diagnosis was tension-type headache.

CT scans in patients affected by acromegaly or sinusitis show a major prevalence of significant morphological differences in the bone and soft tissue of the nasal cavity that cause a deeper and narrower surgical field [21]. The hyper-secretion of GH increased the volume of the turbinate bones and induced an alteration of efflux from the nasal cavity.

In our case, thickening of the bone, hypertrophy of the nasal sinus mucosa and compression of the left cavernous sinus correlated with GH-secreting adenoma caused the acromegalic aspect. GH-secreting adenoma and acromegaly could both be responsible for the entire observed symptomatology, including headache. In fact, symptoms of a possible acromegaly had been observed since 1997, but normal blood levels of GH delayed further endocrinologic and neuroradiologic investigations. Early testing for IGF-1, whose half-life is longer than that of GH, could probably lead to a positive finding not unbiased by the intermittent secretion of GH [22].

During the first clinical phase, headache relapse could possibly be correlated to the increase of IGF-1 rather than to structural abnormalities of the sella turcica. Surgical ablation of the mucous cyst in the maxillary sinus worsened the headache, probably due to a local, non-specific inflammatory reaction. Octreotide administration in the last clinical stage was reported to induce analgesic effects [23].

The peptide, octreotide, induced analgesia with a mechanism that is independent of the inhibition of GH production. Octreotide, in fact, interfered in the synthesis of peptides, such as substance P, by the tumour or by the trigeminal nucleus [24, 25].

In conclusion, the diagnosis of pituitary adenoma remains difficult and is frequently delayed. Using MRI, silent pituitary adenomas are found in 10% of a random adult population [3], while occult adenomas are described in a large range (3%–27%) of post mortem examinations [26].

It is reasonable to hypothesise a GH-producing pituitary adenoma associated with monolateral headache and autonomic signs, mostly involving a direct stimulation of the trigeminovascular system [11]. An additional effect could be linked to the bone and mucosal modifications induced by GH and related hormones in the sinus areas. A large number of observations suggest that the pain and autonomic symptoms, which originated within the cavernous sinus, derived from tumour impairment of the venous drainage [12].

Finally, we emphasise that clinical examination, as well as neuroimaging, remains essential for properly evaluating patients referring with clinical pictures not fulfilling ICHD-II criteria.

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