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CASE REPORT

Cerebral aneurysm and acromegaly: A case report

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ABSTRACT. Few cases are reported concerning the association between cerebral aneurysms and acromegaly, and this is the first case report documenting an increase in diameter of a cerebral aneurysm in persistent acromegaly. Persistently elevated GH plasma levels might promote an increase in diameter of cerebral aneurysms. An accurate follow-up in acromegalic patients is important, especially concerning the cerebrovascular system. Establishing the effectiveness and usefulness of this strategy will require future prospective studies.

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INTRODUCTION

There is a large body of evidence indicating that chronic GH and IGF-I excess has adverse effects on the cardiovascular system (1-3), contributing to the excessive morbidity and mortality in patients with acromegaly (4). This could be explained by the high prevalence of risk factors leading to the atheromatous disease that characterises GH excess, such as hypertension, glucose intolerance and dyslipidemia, which are more frequent in acromegalic patients (5-7). A large retrospective cohort study of mortality incidence in acromegaly has, in fact, shown an increase in mortality rate with longer duration of disease, mainly due to cerebrovascular disease (2). However, only few cases are reported concerning the association between cerebrovascular abnormalities and acromegaly. To the best of our knowledge the present study is the first case report of an acromegalic patient with a cerebral aneurysm, which progressively increased in diameter, concomitantly with persistent GH hypersecretion, and needed surgical clipping.

CASE REPORT

A 61-yr-old man, who had undergone transcranial surgery for clipping of an aneurysm of the right medial cerebral artery (MCA), presented to our Institution for evaluation of a possible persistence of GH hypersecretion.

Family history was negative for hypertension, stroke, diabetes, or multiple endocrine neoplasia 1 (MEN1). The patient had been a smoker until the age of 45 yr and had undergone a left nephrectomy for kidney leyomyomas at the age of 52 yr. Three years before referral to our Unit, the patient had been diagnosed with moderate hypertension and acromegaly (random plasma GH=20.3 μg/l; IGF-I=1285 μg/l) due to a pituitary 8-9 mm microadenoma. Magnetic resonance imaging (MRI) also disclosed an aneurysm of the right MCA of 11 mm in diameter (Fig. 1A and B). The patient underwent surgical adenomectomy from transsphenoidal (TS) approach and immunohistochemistry showed strong staining for GH and PRL, with some LH and TSH positive cells. A conservative management was undertaken for the aneurysm.

At a post-operative (6 months) follow-up visit, the patient had random GH and IGF-I levels of 3.6 μg/l and 336 μg/l, respectively, with normal pituitary gland at MRI (Fig. 1C). On the basis of these data, treatment with SS analogs was recommended. However, the patient refused any therapy, and stopped the follow-up visits. Two yr after TS surgery, the patient presented to the Neurosurgery Unit complaining of headache. Cerebral MRI showed an increase in diameter of the aneurysm of the right MCA, which reached 24 mm (Fig. 1D). Cerebral angiography confirmed the presence of an aneurysm of the distal tract and of the bifurcation of the right MCA, and showed a dural fistula

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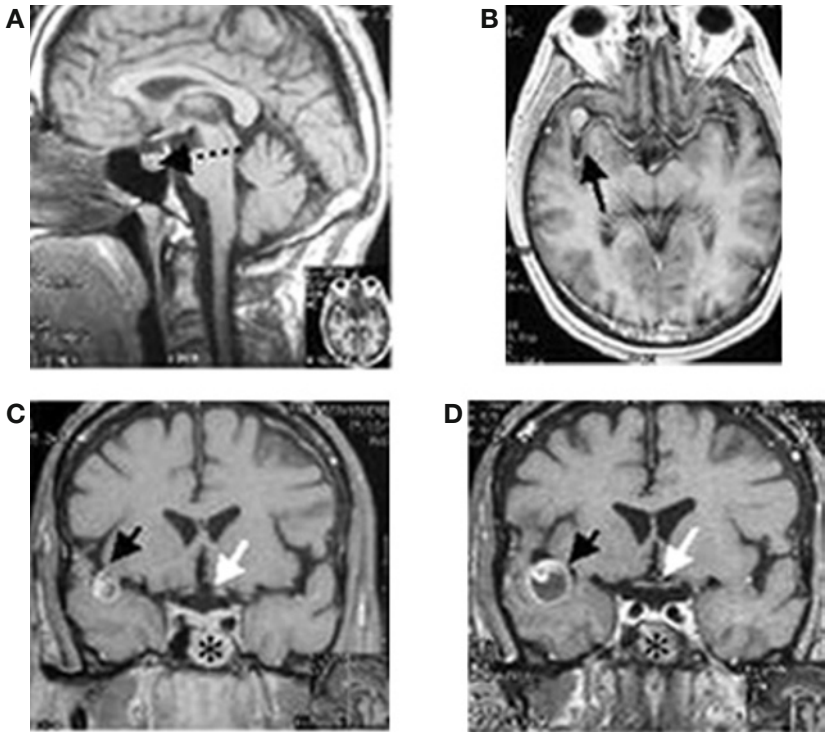

Fig. 1 - Contrast-enhanced T1-weighted magnetic resonance imaging (MRI) images. A) Pre-operative MRI, Sagittal plane: the anterior portion of the pituitary demonstrates a 9 mm low signal microadenoma (dotted black arrow). B) Pre-operative MRI, Axial plane: showing an aneurysm (11 mm, diameter) of the right medial cerebral artery (MCA) (solid black arrow). C) Post-operative MRI image 6 months after transphenoidal (TS) surgery, showing a normal shape and size of pituitary gland (white arrow) and the aneurysm of the right MCA (black arrow). There is an irregular mass (*) in the sphenoid sinus related to the packing adipose tissue. D) Post-operative MRI image 2 yr after TS surgery, demonstrating an increased diameter (24 mm) of the aneurysm of the MCA (black arrow).

of the falx cerebri (Fig. 2A). Therefore, craniotomy for surgical clipping of the aneurysm and closure of the dural fistula was performed. After 2 months, a follow-up angiography showed the absence of the right MCA aneurysm and of the falx cerebri dural fistula (Fig. 2B).

On admission to our Institution, after the MCA aneurysm clipping, the patient presented with classical features of acromegaly. Physical examination revealed blood pressure of 155/90 mmHg, pulse 84 beats/min and slight overweight [body mass index (BMI)= 29 kg/m^2]. The visual field was normal. Hormonal work-up showed a PRL of 2.5 nmol/l, FSH 8 UI/l, LH 6.5 UI/l, testosterone 16 nmol/l, free T_4 0.5 ng/dl, TSH 1.8 µIU/ml, ACTH 5.5 pmol/l, cortisol 345 nmol/l. Persistence of GH excess was diagnosed on the basis of serum GH levels during an 8-h time diurnal course (mean±SEM, 2.6±0.4 µg/l) not suppressible below 1 µg/l after an 75 g oral glucose load, and high IGF-I levels for age (459 µg/l).

By M-mode ultrasonography, an increase in intima-media thickness was demonstrated at level of both common carotid arteries, with well-defined atherosclerotic plaques at the level of the left common and left internal carotid arteries. Two-dimensional M-mode and Doppler echocardiography documented a mild dilatation of the aorta root.

DISCUSSION

The major negative survival determinants in acromegalic patients are elevated GH levels, hypertension, and heart disease (4), which has been widely investigated. However, data on the relationship between GH excess and cerebrovascular disease are still very scant.

The association between pituitary tumors and aneurysms has been previously reported, but it is still unclear whether this association is coincidental (8). There are sporadic case reports of cerebral aneurysm in acromegaly (9-14), and recently a study pointed out that the association of cerebral artery aneurysm with GH-producing adenomas is greater than expected (15). The coexistence of aneurysms and pituitary adenomas has been reported to be more common in GH-secreting tumors, since in a retrospective study considering 150 patients with pituitary adenomas who underwent angiography the incidence of associated aneurysms was as high as 13.8% for GH-secreting adenomas (16).

This is the first report documenting the progressive enlargement of a cerebral aneurysm in a patient with persistently active acromegaly. This case points out the role of GH/IGF-I excess as a risk factor for the development and progression of the cerebrovascular chronic disease.

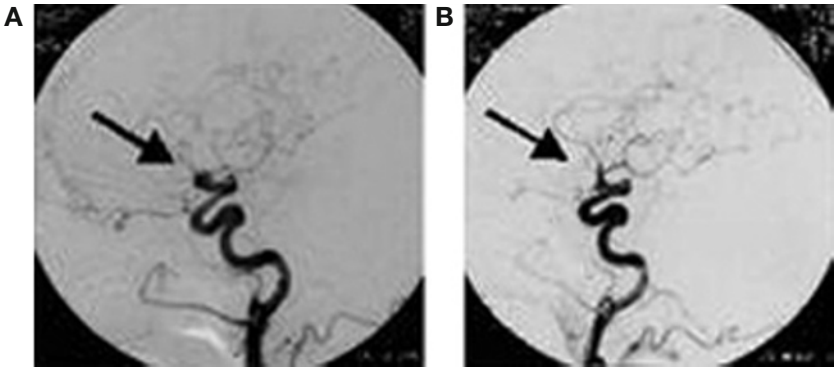

Fig. 2 - Cerebral angiography performed in the patient 2 yr after transsphenoidal (TS) adenomectomy, showing an aneurysm of the distal tract and of the bifurcation of the right medial cerebral artery (MCA) (black arrow) (A), and the surgical cure of the aneurysm (B).

The prevalence rate of asymptomatic aneurysms in the general population has been reported as 0.65-1.3%, with an estimated annual rate of 0.85% for rupture (17), and the size of ruptured aneurysms is significantly larger than that of unruptured aneurysms (18), especially for lesions >10 mm (19). However, the rate of the aneurysm growth is not predictable and does not seem to correlate with hypertension, patient age, or aneurysm location (20), therefore other factors might contribute to the aneurysm enlargement, by acting locally on the vessel walls. In vitro studies showed that IGF-I induces the proliferation of vascular smooth muscle (21), but also vascular nitric oxide generation (22), suggesting that GH may promote opposite effects on vessel walls. No evidence of vascular endothelial dysfunction or structural change was found in acromegalic patients, suggesting that the effects of GH excess on the vessel wall are indirect (23). On the other hand, GH has been shown to influence type I/type III collagen ratio in the arterial walls of rats, leading to an increased stiffness at high load volumes (24). A similar change has been demonstrated in the arterial wall of an intracranial aneurysm of an acromegalic patient (11), suggesting that connective tissue modifications may have a promoting action in the formation of cerebral aneurysms in patients with GH excess.

Whatever the pathophysiological explanation may be, cerebrovascular follow-up could be indicated in patients with acromegaly. In the case reported here, it cannot be excluded that the aneurysmatic lesion could have enlarged regardless of persistence of acromegaly. At the same time, however, a role for the GH/IGF-I axis in promoting the appearance and in contributing to the evolution of the cerebrovascular alteration cannot be ruled out.

The aim of this report is to call attention to cerebral aneurysm in acromegalic patients, who very frequently suffer from hypertension, a condition which has a nearly 7-fold higher risk of aneurysmal subarachnoid hemorrhage (25). Therefore, we suggest that acromegalic patients may benefit from screening for cerebral aneurysm by means of total cerebral MRI, extending the MRI field during pituitary imaging, and, in selected cases, by MR angiography.

Even if the actual incidence of cerebral aneurysms in acromegaly has not yet been determined, increased awareness of a possible association between these diseases may improve the prognosis of acromegalic patients. In order to clarify the possible link between GH excess and cerebral aneurysm formation and/or enlargement, further studies on a large population of acromegalic patients are necessary.

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