CASE REPORT

Biochemical behaviour of an incidentally diagnosed silent corticotroph adenoma

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Abstract

Silent corticotroph adenoma (SCA) is a non-functioning macroadenoma that has positive immunoreactivity for ACTH. Few studies have evaluated the biochemical behaviour of these tumours. We present the case of a 65-year-old male incidentally diagnosed with SCA, in which an exhaustive study of the corticotroph axis was conducted.

INTRODUCTION

Silent corticotroph adenoma (SCA) is a hypophysary adenoma with positive immunoreactivity for ACTH that shows no signs or symptoms of Cushing syndrome (CS) (Kovacs *et al.* 1978). Given the lack of clinical hypercortisolism and the fact that this tumor is usually diagnosed due the existence of clinical signs of compression on structures adjacent to the hypophysis, scant data exist concerning the biochemical behaviour of these tumours (Scheithauer *et al.* 2000; Webb *et al.* 2003; Lopez *et al.* 2004; Baldeweg *et al.* 2005). In recent years, numerous studies have addressed the aetiopathogenesis of these adenomas with conflicting results (Reincke *et al.* 1987; Nagaya *et al.* 1990; Kojima *et al.* 2002). The two most recent hypotheses posit different origins: gonadotroph adenomas (Cooper *et al.* 2010) or corticotroph macroadenomas that produce CS (Tateno *et al.* 2007; Raverot *et al.* 2010). We present the case of an incidentally – and atypically – diagnosed SCA, in which a comprehensive study of the corticotroph axis was conducted.

CASE REPORT

A 65-year-old male, former smoker, with a history of high blood pressure treated with enalapril, was admitted following an acute transient cerebrovascular accident. A cranial CAT scan upon admission revealed no signs of acute cerebral ischaemia detecting instead a sellar mass. Magnetic resonance imaging showed a heterogeneous intrasellar tumour, 23mm in diameter, which eroded the sellar floor and extended to the left cavernous sinus, without chiasmatic compression (Figure 1).

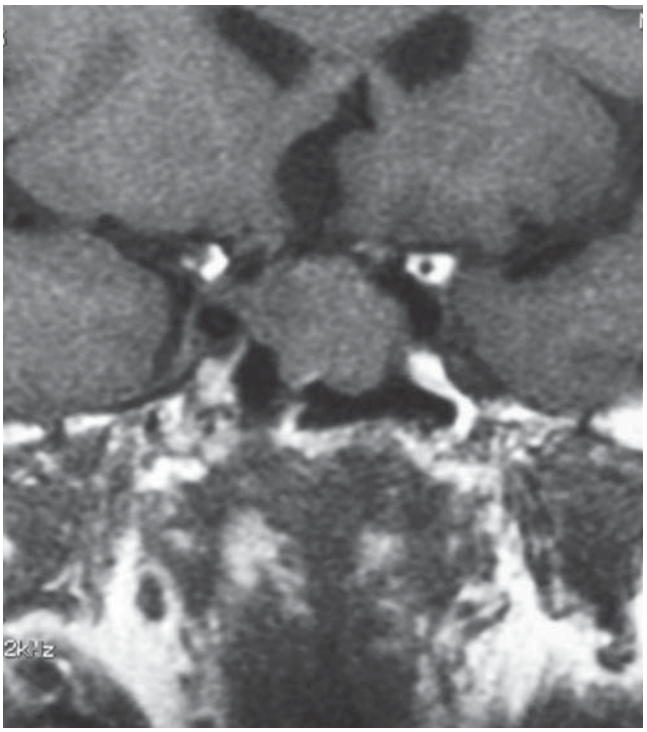

Fig. 1. Nuclear magnetic resonance at the time of diagnosis.

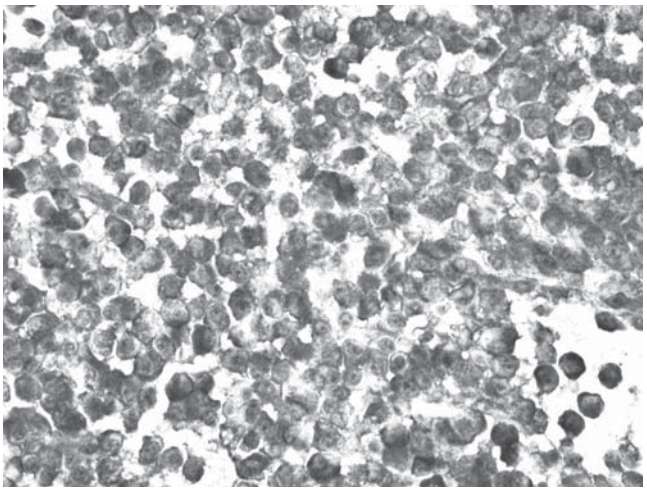

Fig. 2. Immunostaining for ACTH.

On physical examination, the patient had a body mass index of 27.6 kg/m^2 and no signs of endocrinopathies or any other relevant condition.

Baseline pituitary hormonal analysis showed values within a normal range, except for elevated prolactin (500 mcUI/ml; normal 53–360 mcUI/ml) and ACTH levels (137 pg/ml; normal 0.01–46 pg/ml). The study of the corticotroph axis showed two concentrations of 24h urinary free cortisol within normal range (21.5 and 86 mcg/24h; normal 10–90 mcg/24h) and no increase in late night salivary cortisol (1.33 mcg/dl, normal <1.8 mcg/dl). The functional study showed no suppression of cortisol levels with various dexamethasone doses: 1mg overnight, 0.5 mg every 6 hours for 2 days, and 8 mg overnight (Table 1).

Tab. 1. Functional study of the corticotroph axis before the surgery.

	Basal values	Post-suppression values	Normal values
Suppression with 1 mg overnight dexamethasone			
Cortisol	21 mcg/dl	18.6 mcg/dl	<5 mcg/dl
ACTH	99 pg/ml	97 pg/ml	0.01–46 pg/ml
Suppression with 0.5 mg dexamethasone every 6h for 2 days			
Cortisol	21.5 mcg/dl	14.1 mcg/dl	<1.8 mcg/dl
24h urinary cortisol	68.3 mcg/24h	70.4 mcg/24h	<10 mcg/24h
ACTH	112 pcg/ml	127 pg/ml	0.01–46 pg/ml
Suppression with 8 mg overnight dexamethasone			
Cortisol	26.3 mcg/dl	9.72 mcg/dl 63% suppression	<5 mcg/dl, or suppression >80%
ACTH	99 pg/ml	97 pg/ml	

Legend: ACTH: Adrenocorticotropic hormone

Following transphenoidal resection of the tumour, the patient experienced no post-operative complications, presented no symptoms suggesting suprarenal insufficiency and required no changes in the treatment used to control his blood pressure. The anatomo-pathological study showed a hypophysary adenoma with an immunohistochemistry very positive for ACTH and negative for all other hormones (Figure 2).

The hormone study two months after surgery showed normalized ACTH (25 pg/ml) and prolactin levels, and the values of the other basal hypophysary hormones within normal range. Suppression was achieved with 1mg dexamethasone, with post-inhibition cortisol of 2.5 mcg/dl. Follow-up nuclear magnetic resonance two years after surgery showed the sellar area occupied by heterogeneous tissue, compatible with blockage material, scarring changes, and glandular residues.

DISCUSSION

Silent corticotroph adenoma (SCA) is defined as a hypophysary adenoma with positive immunoreactivity for ACTH developing without any of the clinical or analytical characteristics of hypercortisolaemia. In 1978, Kovacs *et al.* (1987) became the first to postulate the existence of this type of adenoma. Two years later, in a series of surgically resected adenomas, Hovath *et al.* (1980) described in greater detail 17 cases with positive immunoreactivity for ACTH that did not present with hypercortisolism, from which 3 anatomopathological subtypes could be described. One of these subtypes was later redefined as "silent type 3 adenoma", and now 2 SCA subtypes are recognized (Scheithauer *et al.* 2000): Type I adenomas, indistinguishable from the adenomas that cause CS, are basophilic, PAS-positive, and have

a granulated pattern; type II are slightly basophilic, with a chromophobic PAS stain and a diffuse pattern. Although in the majority of cases the immunohistochemistry is only positive for ACTH, cases with co-expression of prolactin and GH have been described (Abe *et al.* 2001, Kageyama *et al.* 2007).

SCA represents about 5% of non-functioning adenomas in surgical series of sellar tumours (Baldeweg *et al.* 2005; Saeger *et al.* 2007) and about 20% of all corticotroph tumours (Lopez *et al.* 2004; Sahli *et al.* 2006). The average age at onset is approximately 50 years and there is no sex correlation (Scheithauer *et al.* 2000; Schaller *et al.* 2003; Webb *et al.* 2003; Lopez *et al.* 2004; Baldeweg *et al.* 2005; Sahli *et al.* 2006; Saeger *et al.* 2007)

In contrast to hypophysary adenomas that cause CS, SCAs are not associated with the clinical symptoms of hormone hypersecretion; they are normally diagnosed from compressive symptoms, and therefore incidental diagnosis as in this case is exceptional (Scheithauer *et al.* 2000; Sahli *et al.* 2006). At the biochemical level, researchers have observed normal levels of basal plasmatic and 24h urinary free cortisol, with slightly elevated ACTH (Scheithauer *et al.* 2000; Kojima *et al.* 2002; Webb *et al.* 2003;L Tateno *et al.* 2007). Since its first description more than 30 years ago, various theories have attempted to explain the absence of hypercortisolism in these hypophysary tumours: 1) ACTH secretion that is insufficient to produce hypercorticism, 2) enhanced ACTH catabolism by lysosomes(Scheithauer *et al.* 2000), 3) secretion of inactive forms of ACTH (Reincke *et al.* 1987; Nagaya *et al.* 1990), and 4) reduced number of ACTH-producing cells(Kojima *et al.* 2002). Recent studies that have attempted to explain the origin and behaviour of SCAs yielded conflicting results, with some suggesting a common aetiopathogenesis with gonadotroph adenomas(Cooper *et al.* 2010) and others postulating a shared origin with corticotroph macroadenomas that cause CS (Tateno *et al.* 2007; Raverot *et al.* 2010). For example, Cooper *et al.* (2010) describe similar clinical characteristics at the time of diagnosis in SCA and non-functioning gonadotrophon adenomas as well as increased expression of gonadotroph markers (AX-1 and SF-1). These characteristics set them apart from adenomas causing CS. It must be stressed that this study does not make a distinction between macro and microadenomas. On the other hand, Raverot *et al.* (2010) observed that, in contrast to microadenomas causing CS, macroadenomas (i.e., SCA and macroadenomas causing CS) are similar in histological and epidemiological terms (both diagnosed on the fifth decade of life, showing the same prevalence for both sexes and with a higher recurrence rate than microadenomas). Both macroadenomas present weak PC1/3 expression and a low cortisol/ACTH ratio suggesting abnormalities in POMC processing. Raverot *et al.* (2010) hypothesized that these two types of tumour are not intrinsically different, with hypercortisolism arising only when levels of low-activity ACTH are severely increased.

The lack of signs and symptoms of hypercortisolism, along with the appearance of acute compressive symptoms requiring immediate neurosurgery, explain the lack of published information about the behaviour of the corticotroph axis. This is the first time the response of these tumours to suppression testing with differing doses of dexamethasone has been documented. The lack of suppression, both at low doses and high doses of dexamethasone, suggests a change in the negative feedback of these tumours similar to what is found in SC-producing macroadenomas. These data support the hypotheses that postulate a common aetiopathogenic origin for SCA and macroadenomas that cause CS. We wish to point out that in the series published by Cooper *et al.* (2010) no distinction was made between micro and macroadenomas that cause CS when comparing the expression of gonadotropic markers with respect to SCA and gonadotropic adenomas. This could have influenced the results, and we believe that these types of adenomas should be analysed separately in future research. Additional studies assessing the effect of varying doses of dexamethasone shall be needed in order to confirm our findings.

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