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 hypophyseal 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 aetio-pathogenesis 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).
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On physical examination, the patient had a body mass index of 27.6 kg/m² 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 mcU/ml; normal 53–360 mcU/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).

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

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<th>Table 1. Functional study of the corticotroph axis before the surgery.</th>
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<td><strong>Basal</strong></td>
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Legend: ACTH: Adrenocorticotropic hormone
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. The lack of 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 aetiological 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 gonadotrophic 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.

REFERENCES


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