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Inconsistent Stimulation of Plasma ACTH Through Corticotropin-Releasing Factor in a Patient with Central Cushing's Disease due to Pituitary Adenoma

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Summary. Three uncommon findings were observed in a case of Cushing's disease due to macroadenoma: no suppression of plasma ACTH during an 8-mg dexamethasone test, a negative corticotropin-releasing factor test, and a normal X-ray of the sella turcica. Despite these findings, the diagnosis of pituitary was confirmed Cushing's syndrome by computerized tomography and a transphenoidal operation.

Key words: Corticotropin-releasing factor (CRF) – Cushing's disease – ACTH

Verification of hypercortisolism and differentiation of central, peripheral, and paraneoplastic CS is usually achieved by means of 2-mg and 8-mg dexamethasone tests, together with determination of plasma ACTH. The latter may have to be sampled selectively at different sites, if ectopic ACTH production is suspected [8].

The positive response in the CRF test has become an important alternative to the lysin-vasopressin test [6, 7] in central CS. However, our case illustrates that the various function tests did not help in the diagnosis of a case of pituitary CD with macroadenoma, which was diagnosed only by CT.

Case Details

A female patient, 44 years of age, had had an appendectomy in 1956 and a thyroid adenoma surgically removed in 1961. Since 1981, she had gained weight, especially in the cervical and facial regions, and since 1982 had had irregular menstruation. When examined, she was 165 cm tall and weighed 65 kg. Distinct CS stigmata were evident ("moon" face, "buffalo" hump, truncal obesity, and hirsutism), and her blood pressure was 200/100 mm Hg. Laboratory findings were normal, except for leucocytosis with relative lymphopenia and a blood sedimentation rate of 46/86. The results of the hormonal function tests are shown in Table 1.

All other tests of pituitary function, such as LH, FSH, prolactin (even under stimulation), as well as testosterone and thyroid hormone determinations, showed no pathological results. A CRF test (synthetic ovine CRF from Bachem Inc., Bubendorf, Switzerland; prepared as described pre-

Abbreviations: CRF = corticotropin releasing factor; CD = Cushing's disease; CS = Cushing's syndrome; CT = computerized tomography; GH = growth hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; LH-RH = luteinizing hormone releasing hormone

Table 1. Preoperative hormonal investigations

Urinary excretion/24 h	17-Ketosteroids 50.1 mg	17-Hydroxycorticoids 20.0 mg	
	Plasma ACTH	Serum cortisol	
	at 8 a.m.	8 a.m.	4 p.m.
	139 pg/ml	255	260 ng/ml
Normal ranges	<80 pg/ml	150–250	30–150 ng/ml
	Serum cortisol at 8 a.m.		
After 2-mg dexamethasone	201 ng/ml	Normal: <20 ng/ml	
After 8-mg dexamethasone	282 ng/ml		

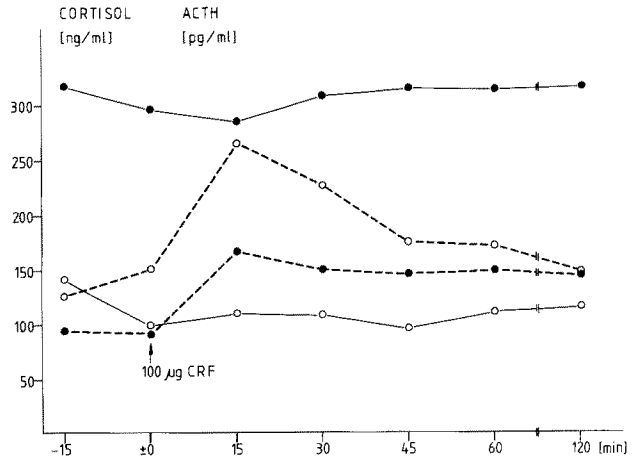

Fig. 1. ACTH (o) and cortisol (•) responses to 100 µg CRF before (o•——o•) and after (o•---o•) transphenoidal adenomectomy because of Cushing's disease. (For details, see text)

viously [2]) produced no stimulation of the ACTH[1] and cortisol values (Fig. 1).

Radiological Examinations

Normal findings were observed on conventional X-ray films of thorax and cranium, tomograms of hilus and sella turcica, and pyelograms. An abdominal CT showed: normal kidneys and pancreas; adrenal glands of regular outline that were large but still within the normal range. A cranial CT showed a large, partially cystic, pituitary adenoma infiltrating the sphenoidal sinus.

No defects were found in the visual fields.

Progress

The pituitary adenoma was removed selectively, and probably subtotally by the transnasal route. A large tumour was found, which had developed from a mostly intact sella in the subarachnoidal space and the sphenoidal sinus. Histologically, the tumour was an undifferentiated mucoid cell-adenoma showing signs of infiltration of the bone and subarachnoidal space. Immunostaining revealed 20% ACTH-positive cells. After adenomectomy, plasma ACTH and cortisol levels slowly decreased, and the symptoms of CS disappeared. Two months later, the morning cortisol level was 89 ng/ml, while the ACTH level was still slightly elevated (120 pg/ml). The patient now suffered from neuralgia, tiredness, and morning depression. Pituitary functions were controlled with an LH-RH ACTH-stimulation test, with normal values for cortisol, LH, FSH, prolactin, and GH.

The CRF test now resulted in normal stimulation of ACTH and cortisol (Fig. 1). Because of persistently increased ACTH levels, the sella region was prophylactically irradiated (60 Gy).

Discussion

This case clearly illustrates some difficulties in the diagnosis of hypercortisolism. We confirm that the failure of 8-mg dexamethasone to suppress ACTH does not exclude pituitary CS [1] in all cases.

The negative CRF test before adenomectomy remains unexplained, as there is usually a significant increase of ACTH and cortisol within the first hour of the test in patients with central CS [2, 6, 7, 9]. Improper application of CRF is an unlikely explanation, since the patient showed the usual symptoms of flush and heat waves during both tests [7, 9].

The case history makes a paraneoplastic activity improbable. A pituitary carcinoma producing ACTH is not supported by the histological findings and by the only slightly increased ACTH levels; the infiltrative character of the adenoma and the cell type is also noted.

The size of the tumour responses in the lysin-vasopressin and CRF tests far exceeded the normal stimulation values reported for large ACTH-producing adenomas [3, 6]. The patient's tumour produced only slightly elevated ACTH levels, in spite of its size, and showed no reaction to CRF.

In addition, we hypothesise that the CRF-sensitive ACTH-producing cells of the normal pituitary tissue became suppressed, preoperatively, under the influence of the tumour. The postoperative stimulation values may represent normal pituitary. However, this explanation is in contrast with the finding that the ACTH secretion of the paraadenomatous pituitary is regularly suppressed after adenomectomy in CD [4]. More likely, the small remainder of the adenoma was changing in receptor sensitivity to CRF after reduction of the cortisol excess. Finally, this case history indicates that despite finding a normal sella structure in a conventional X-ray picture, there may still be a macroadenoma of the pituitary. It is therefore advisable to include a CT of the pituitary region in the primary program.

1 The determination of ACTH by radioimmunoassay [5] by Dr. Klingler, Inst. für Biochem. Endokrinol., Med. Hochschule Lübeck, is gratefully acknowledged

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Note Added in Proof

The problem that the CRF test does not produce ACTH and cortisol elevations in all patients with Cushing's disease has previously been described by Pieters et al. (Pieters GFFM, Hermus ARMM, Smals AGH, Bartelink AKM, Benraad TH J, Kloppenborg PWC (1983). Responsiveness of the Hypophyseal-Adrenocortical Axis to Corticotropin – Releasing Factor in Pituitary-Dependent Cushing's Disease. J Clin Endocrinol Metab 57:513–516)