NOTE

Anterior Pituitary Function in Cushing's Syndrome: Study of 36 Patients

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Abstract. We studied the anterior pituitary function in 36 patients (25 females and 11 males, mean age: 35 years) with untreated Cushing's syndrome by simultaneous triple stimulus with insulin, TRH and LHRH. Thirty-one patients (86%) had Cushing's disease and five (14%) had an adrenal adenoma. We observed a lack of response of GH to hypoglycemia in 88%, TSH to TRH in 91%, LH to LHRH in 30%, FSH to LHRH in 12% and PRL to TRH in 6% of the patients. Low-to-normal total thyroxine (T4) values were obtained in 37%, with low triiodothyronine levels in 87%. The free-T4 index was normal in all patients. Total testosterone was low in only one adult man, while estradiol and progesterone were low in 45% and 15% of premenopausal women, respectively. We observed no differences in either axis among patients with Cushing's syndrome of different etiologies. Nor was there any statistical difference between the frequency of alteration of each axis and the levels of urinary free cortisol or the duration of the disease. We conclude that hypercortisolism is responsible for the abnormalities in anterior pituitary function in Cushing's syndrome.

Keywords: Cushing's syndrome, Pituitary function, Hypercortisolism.
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THE PRESENCE of abnormalities in anterior pituitary function in patients with Cushing's syndrome was first reported some time ago. Some authors have proposed a primary hypothalamic or central nervous system dysfunction in those individuals with Cushing's disease [1, 2]. However, the presence of these abnormalities in Cushing's syndrome secondary to adrenal adenoma and the reversibility of the pituitary malfunction after selective adenomectomy in patients with Cushing's disease point to hypercortisolism as the cause of these abnormalities [3, 4]. Moreover, it is known that with the exogenous administration of glucocorticoids, the anterior pituitary gland can mimic the dysfunction seen in patients with Cushing's syndrome [5].

This report deals with the analysis of endocrine function prior to treatment in 36 patients with Cushing's syndrome, especially emphasizing the study of the thyroid and gonadal axes.

Patients and Methods

The anterior pituitary function in 36 patients with Cushing's syndrome was assessed prior to treatment. Thirty-one cases were due to Cushing's disease and five to adrenal adenomas. We excluded the patients with ACTH-producing pituitary macroadenomas. Twenty-five subjects were females and eleven were males, ranging in age from 7 to 65 yrs, with an average age of 35 yrs. The four children included in our series had retarded growth. Among the adult males, eight had Cushing's disease and one an adrenal adenoma.
ma. Among the 23 adult females, 19 had Cushing’s disease and the remaining 4 had adrenal adenoma. None of our patients had symptoms of thyroid malfunction. Six males complained of impotence. Two women with adrenal adenoma had amenorrhea. Of the 19 women with Cushing’s disease, 10 had amenorrhea and 6 had cyclic menses. (We have excluded from the analysis of gonadal function 2 postmenopausic women and 1 hysterectomized subject).

Diagnosis was reached on the basis of clinical findings and routine laboratory tests, as well as abdominal and sella turcica CT scan. The basal level of 24-h urinary free cortisol (UFC) ranged from 120 to 2032 µg/day (mean ± SD: 464.7±384.8 µg/day). The duration of the disease was from 0.5 to 13 yrs (mean ± SD; 4.36±3.3 yrs).

We studied the responsiveness of the anterior pituitary gland to simultaneous stimulation with insulin (0.2 IU/kg, iv), TRH (200 µg iv) and LHRH (100 µg iv). The hypoglycemic stimulus was considered adequate if the plasma glucose level fell below 40 mg/dl, and this was achieved in all cases.

Blood samples for GH were drawn at 0 time and 30, 60 and 90 min after stimulus. Blood samples for TSH, PRL, LH and FSH were obtained at 0, 20, 40 and 60 min after stimulation.

In women with cyclic menses, all gonadal axis hormones were obtained during the follicular phase of the cycle.

Basal levels of serum total thyroxine (T4), total triiodothyronine (T3), estradiol (E2), progesterone (P) and total testosterone (Te) were measured by radioimmunoassays. The free T4-index (FT4I) was calculated on the basis of the RT3 uptake. The free T4-index (FT4I) was calculated on the basis of the RT3 uptake.

Results were analyzed by parametric (Pearson’s correlation test) and non-parametric contrast tests (Kruskall-Wallis and Mann-Whitney) in which p<0.05 was considered significant.

Informed consent was obtained from all the patients. The study was approved by the Institutional Review Board of our hospital.

**Results**

A serum GH in excess of 7 ng/ml was considered to indicate a normal response to hypoglycemia. An increase in TSH of 5 to 25 µU/ml and a 3 to 5-fold increase in PRL after TRH administration were considered normal. Finally, we considered a more than three-fold rise in LH and a 1/2 to 2-fold rise in FSH, after LHRH stimulus, to be normal responses. Hyperresponsiveness was considered when the increases were more than ten-fold and five-fold in LH and FSH, respectively, after LHRH.

In 88% of patients (30/34), the GH did not respond to hypoglycemia.

Serum T4 was low in one patient, but was at a low-to-normal level (≤6 µg/dl) in 11 (37%). The FT4I was normal in all cases. Serum T3 was low in 87% of patients (26/30), and basal TSH was low (normal range: 0.2–5 µU/ml) in only 3 patients, and did not respond to TRH stimulus in 91% of patients (32/35).

The only man with an adrenal adenoma was impotent, and had a low Te level, with normal response of LH and hyperresponsiveness of FSH to LHRH. All adult males with Cushing’s disease had normal Te, although five complained of impotence. LH response after LHRH stimulation was normal in 5 patients, high in 2 and low in 1 subject. FSH response to LHRH was low in one patient.

All the women with adrenal adenomas had normal E2 and P levels. LH response to LHRH was normal in patients with cyclic menses, and low and high in one each of two women with amenorrhea. FSH response to LHRH was low in one patient.

Among the adult women with Cushing’s disease, the determinations of E2 and P were low in 9 and 3
Table 1. Comparison of pituitary response (mean and peak values) and basal thyroid and gonadal hormones in patients with Cushing's disease and adrenal adenoma

<table>
<thead>
<tr>
<th></th>
<th>Cushing's disease</th>
<th>Adrenal adenoma</th>
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<tbody>
<tr>
<td></td>
<td>( \bar{x} ) basal</td>
<td>( \bar{x} ) peak</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>0.56 (0.25–1.9)</td>
<td>3.69 (0.35–29)</td>
</tr>
<tr>
<td>TSH (( \mu U/ml ))</td>
<td>2.79 (0.1–3.1)</td>
<td>3.56 (0.12–6.8)</td>
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<tr>
<td>LH (mU/ml)</td>
<td>5.08 (0.49–29)</td>
<td>19.87 (1.4–76)</td>
</tr>
<tr>
<td>FSH (mU/ml)</td>
<td>9.88 (0.5–75)</td>
<td>18.54 (3.3–88)</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>8.93 (2.8–25)</td>
<td>37.98 (13.8–105.8)</td>
</tr>
<tr>
<td>T4 (( \mu g/dl ))</td>
<td>6.81 (3.1–11.1)</td>
<td>6.34 (4.1–7.7)</td>
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<tr>
<td>FT4I</td>
<td>6.72 (4.6–10.1)</td>
<td>7.15 (6.6–7.7)</td>
</tr>
<tr>
<td>T3 (ng/ml)</td>
<td>0.71 (0.4–1.4)</td>
<td>0.57 (0.3–0.8)</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>64.37 (10–390)</td>
<td>110.3 (108–115)</td>
</tr>
<tr>
<td>P (ng/ml)</td>
<td>1.31 (0.1–8.8)</td>
<td>2.53 (0.3–7)</td>
</tr>
<tr>
<td>Te (ng/ml)*</td>
<td>4.26 (0.66–6)</td>
<td>3.3 (1.6–5)</td>
</tr>
</tbody>
</table>

T4, total thyroxine; FT4I, free T4-index; T3, total triiodothyronine; E2, estradiol; P, progesterone; Te, total testosterone (*only males).

patients, respectively. The LH response to LHRH was normal in 6, low in 3 and high in 4 patients, while that of FSH was normal in all of them.

Basal PRL levels were normal in all patients, and only failed to respond to TRH stimulus in 6% of the group (5/31).

No statistically significant differences were seen between the lack of response of the different axes and the level of UFC and the duration of the disease (t), or between UFC and t. Pituitary function (Fig. 1) and basal thyroid and gonadal hormones in patients with Cushing's disease and those with adrenal adenoma are compared in Table 1.

Discussion

There have been many reports on GH secretion in Cushing's syndrome, showing a decreased response to different stimuli (insulin, vasopressin and arginine [6]. In the majority of patients with Cushing's disease in whom hypercortisolism has been corrected after transphenoidal removal of pituitary microadenomas or bilateral adrenallectomy, GH responsiveness has been normalized, making it unnecessary to postulate an intrinsic defect in the hypothalamic control of GH secretion [7, 8].

In our study, we have found a high percentage of lack of response of GH to hypoglycemia, which was similar in patients with Cushing's disease and those with adrenal adenomas.

In patients with Cushing's syndrome, the TSH response to TRH is usually impaired, the dose of TRH given in the stimulus being important. Some authors obtained a subnormal TSH response to TRH after short-term, high-dose and long-term,
low-dose glucocorticoid (GC) administration, suggesting a suppressive action of the GC at the pituitary or suprahypophyseal level [9]. Low-to-normal T4, with low T3 and thyroid binding globulin (TBG) levels are frequently observed in Cushing's syndrome or during chronic GC administration. This results in a new equilibrium characterized by a normal free T4 level. Because production of T3 is mostly extrathyroidal in normal persons, the pronounced lowering of serum T3 is due to the GC suppressive effect on peripheral T4 monodeiodination [10].

The high percentage of TSH non-responders in our study may be due to the low dose of TRH used in the test. Although only one patient had a low T4 level, the FT4I was normal in all patients, showing that the decrease in TBG was responsible for that. We observed no differences between the lack of response of TSH to TRH in patients with Cushing's disease and those with adrenal adenoma.

Amenorrhea in females and decreased libido and potency in males are frequently present in patients suffering from Cushing's syndrome. Several reports support the presence of a hypogonadotropic hypogonadism in males and females due to a direct inhibiting action of the adrenal steroids at the pituitary or hypothalamus level [11, 12]. In contrast to the reduced LH response, that of FSH was relatively well maintained.

Odagiri et al. studied the gonadal axis in women with Cushing's syndrome, finding lower E2 levels, and higher LH and FSH response after LHRH in patients with adrenal adenomas than in women with pituitary microadenomas, suggesting that the gonad was the primary site of suppression in patients with adrenal adenoma [13].

In our study, we have found no differences between patients with Cushing's syndrome of different etiologies in the presence of basal levels of gonadal steroids, nor with respect to responsiveness of LH and FSH to LHRH. However, we have observed that the lack of response of LH to LHRH was more frequent (30%) than of FSH to LHRH (12%). Similar results in gonadal function have been reported by others [14]. Some studies have reported a low PRL response to metoclopramide in patients with Cushing's syndrome that was resolved after the elimination of hypercortisolism [15]. Other authors showed that short-term administration of high-dose glucocorticoids blunted the PRL response to TRH in normal men [5]. We have found that the PRL response to TRH was normal in the majority of our patients.

Finally, we can conclude that the secretory regulation of the anterior pituitary hormones is frequently altered in patients with Cushing's syndrome, this being observed both in patients with Cushing's disease and those with adrenal adenoma, finding which points to hypercortisolism as the cause of the dysfunction. The sensitivity of the different axes is variable, with GH and TSH being the most frequently altered. There were no statistical differences between the frequency with which the different axes were altered and the levels of UFC or the duration of the disease.

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References


