Hypercortisolism with non-pigmented micronodular adrenal hyperplasia: transition from pituitary-dependent to adrenal-dependent Cushing’s syndrome

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We report on a female patient with Cushing’s syndrome in whom we observed the transition from pituitary dependency to adrenal dependency. Basal ACTH and cortisol values, the CRH test, the dexamethasone suppression test as well as CT of the pituitary and the adrenal gland all reflected pituitary-dependent Cushing’s disease in 1985. The patient refused treatment, but presented again five years later. At that time ACTH was suppressed before and after CRH injection. Plasma cortisol did not respond to CRH. After ketoconazole therapy, ACTH was within the high normal range. The patient underwent bilateral adrenalectomy. The adrenals exhibited a bilateral micronodular hyperplasia of the zona fasciculata. In vitro examination of adrenal cells revealed a maintained ACTH response. Some weeks postoperatively, the patient died from pneumonia. Histological examination later showed a chromophobe pituitary microadenoma; ACTH was demonstrated immunohistologically in the adenoma. We postulate that some cases of pituitary Cushing’s disease initially exhibit a bilateral homogeneous adrenal hyperplasia which then develops into a nodular hyperplasia; in the next stage of the disease, single micronodules may become autonomous and elevated cortisol levels suppress ACTH secretion of the pituitary adenoma.

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Pituitary-dependent hypercortisolism with bilateral adrenal hyperplasia is the cause of non-iatrogenic Cushing’s syndrome in about 70 to 80% of cases. Bilateral homogeneous adrenal hyperplasia is generally seen, but micro- or micronodular hyperplasia of both adrenal glands is found in 20 to 40% of the patients with Cushing’s disease (1). Solitary adrenal macroadenomas or macronodules were observed in some patients with pituitary-dependent Cushing’s disease (2–5). It was postulated that prolonged ACTH stimulation leads to nodular adrenal hyperplasia and that some of the macronodules may become autonomous (1, 6). We present a case in which the transition from clearly pituitary-dependent Cushing’s disease to partial autonomy of the adrenals without formation of macronodules was observed in the natural course of the disease.

Case report

A 65-year-old woman was hospitalized because of pneumonia in 1985. The previous history revealed a brain infarct in 1980, non-insulin-dependent diabetes mellitus and arterial hypertension since 1981. We saw a febrile patient (height 156 cm, weight 60 kg) with a round, reddish face, bull-necked, marked muscular atrophy of the extremities, adiposity of the trunk and hirsuitism. Pulse 92/min, blood pressure 140/90 mmHg, left-basal pulmonary dampening and moist rales. The heart and abdomen were normal. X-rays showed an infiltrate in the left lower lobe of the lung. Leucocytes were 14.8 × 10⁹/l on admission, otherwise normal red and white blood picture. Sodium, potassium, creatinine, CAT, GPT, alkaline phosphatase, uric acid, bilirubin and gamma-GT, were within the normal range. Fasting blood glucose was 12.1 mmol/l.

After recovery from pneumonia, dexamethasone suppression tests at 1 and 8 mg (overnight single dose in each test), cortisol excretion in 24 h urine and a h-CRH test were typical for pituitary-dependent Cushing’s disease (Tables 1 and 2). An overnight single-dose metyrapone test showed the following responses: 8.46 pmol/l ACTH, 374 nmol/l cortisol and 422 nmol/l 11-deoxycortisol at 08.00 (normal: ACTH > 37.4 pmol/l, 11-deoxycortisol > 200 nmol/l). Cranial CT was compatible with a pituitary microadenoma. Abdominal-CT showed slight bilateral homogeneous adrenal hyperplasia. The patient refused further endocrinological diagnostic measures and treatment and left the clinic. She became bedridden in 1988 due to progressive muscular atrophy, osteoporosis and back pain. Diabetes mellitus has...
required insulin treatment since May 1990. In July 1990, the patient was rehospitalized because of hypoglycemia. The CRH test in 1990 showed no stimulation of cortisol. Plasma ACTH was always below the detection limit (<1.65 pmol/l). Cortisol suppression after 8 mg dexamethasone (overnight) was still compatible with pituitary Cushing’s disease. Basal TSH was 1.8 mU/l, T3 1.8 nmol/l, T4 94 nmol/l, FSH 1.8 µg/l, LH <0.1 µg/l (normal values, postmenopausal: FSH >10 µg/l, LH > 10 µg/l), testosterone 0.732 nmol/l, estradiol 132.2 pmol/l and DHEAS 0.33 mg/l. The patient received 2 x 200 mg ketoconazole/day for five days until surgery. The pituitary MRI revealed a 5 mm intrasellar space-occupying lesion that had already been visualized by CT in 1985. The abdominal CT showed slight bilateral adrenal hyperplasia with at least two small nodules in the right adrenal gland. The patient underwent bilateral adrenalectomy. Pneumonia and respiratory failure developed postoperatively. The patient was intubated for 17 days and died 21 days after adrenalectomy.

Materials and methods

Histology of the pituitary: paraffin sections, hematoxylin-eosin (HE) and Goldner staining and special immunohistological staining of PRL, hGh, FSH, TSH, LH and ACTH by the APAAP and ABC method. HE staining of the adrenals. Adrenal cells were isolated as described recently (7). Plasma cortisol was measured by a solid-phase radioimmunoassay using a CEA-Sorin kit (Italy). Plasma 11-desoxycortisol was measured after paper chromatography by radioimmunoassay (8, 9). Urinary free cortisol was measured after partial purification by high-performance liquid chromatography (8, 9). Plasma ACTH was measured in unextracted plasma using a kit purchased from CEA-Sorin. The lowest detectable plasma ACTH concentration varies between 1.10 and 2.20 pmol/l (8).

Results

Dynamic endocrine testing in 1985 and 1990

Dexamethasone suppression testing and the CRH test in 1985 were compatible with pituitary Cushing’s disease (Tables 1 and 2). In 1990, on the other hand, CRH did not stimulate the pituitary-adrenal axis. ACTH remained below the detection limit, and plasma cortisol was not increased (Table 1). Remarkably, the dexamethasone suppression test (8 mg) in 1990 was still compatible with pituitary Cushing’s disease (Table 2).

Cortisol excretion in 24 h urine was 358.7 and 341.4 nmol in 1985. In 1990 the cortisol excretion was only 185 and 199 nmol (the normal range is 30–130 nmol in 24 h urine) and decreased to 61 nmol in 24 h urine during suppression with 32 mg dexamethasone. Repeated measurement of plasma ACTH in 1990 showed ACTH to be below the detection limit on four occasions and just detectable twice at 3.13 and 3.24 pmol/l.

Effect of ketoconazole treatment

In 1990, the patient received 2 x 200 mg ketoconazole/day for five days. On day 5, before intake of the morning dose of ketoconazole, plasma ACTH was 6.78 pmol/l, plasma cortisol 329 nmol/l; 3 h after intake of the morning dose, ACTH was 9.76 pmol/l, cortisol 222 nmol/l. Cortisol excretion in 24 h urine on days 4 and 5 of ketoconazole treatment had decreased to 11 and 22

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**Table 1.** Response of plasma ACTH and plasma cortisol to corticotropin-releasing hormone (1985 and 1990).

<table>
<thead>
<tr>
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<th>15</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
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</thead>
<tbody>
<tr>
<td>ACTH 1985 (pmol/l)</td>
<td>2.62</td>
<td>2.42</td>
<td>3.46</td>
<td>2.89</td>
<td>2.84</td>
<td>2.9</td>
</tr>
<tr>
<td>ACTH 1990 (pmol/l)</td>
<td>&lt;1.65</td>
<td>&lt;1.65</td>
<td>&lt;1.65</td>
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<tr>
<td>Cortisol 1985 (nmol/l)</td>
<td>303</td>
<td>350</td>
<td>786</td>
<td>722</td>
<td>656</td>
<td>612</td>
</tr>
<tr>
<td>Cortisol 1990 (nmol/l)</td>
<td>471</td>
<td>370</td>
<td>392</td>
<td>380</td>
<td>392</td>
<td>285</td>
</tr>
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At 11.00 (0 min) the patient received an intravenous bolus of 100 µg of h-CRH.

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**Table 2.** Response of plasma ACTH and plasma cortisol to dexamethasone in 1985 and 1990.

<table>
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<tbody>
<tr>
<td>Basal</td>
<td>4.23</td>
<td>&lt;1.65</td>
<td>1052</td>
<td>609</td>
</tr>
<tr>
<td>1 mg dexamethasone</td>
<td>2.53</td>
<td>&lt;1.65</td>
<td>706</td>
<td>691</td>
</tr>
<tr>
<td>8 mg dexamethasone</td>
<td>2.33</td>
<td>&lt;1.65</td>
<td>189</td>
<td>171</td>
</tr>
<tr>
<td>32 mg dexamethasone</td>
<td>—</td>
<td>&lt;1.65</td>
<td>—</td>
<td>94</td>
</tr>
</tbody>
</table>

The patient received dexamethasone for the 1 and 8 mg test at 24 h in each case. ACTH and cortisol were determined the following morning at 08.00. For the 32 mg test, the patient was given 8 mg at 6 h intervals for 24 h. ACTH and cortisol were determined at 08.00 the following morning.
Few immunohistologically (Fig. 1) without producing evidence of ACTH-producing cells. The residual pituitary was otherwise without pathological findings and had a normal pattern. Few ACTH-producing cells could be demonstrated immunohistologically in the residual pituitary gland (Fig. 2A and B).

Effects of angiotensin II and ACTH on adrenocortical cells in vitro

The basal cortisol production rate was 123.5 ± 8.6 ng/10\(^3\) cells (mean of four independent experiments ± SEM; normal: 23–225 ng/10\(^3\) cells as described recently (7)). Stimulation of cortisol secretion was achieved at an ACTH concentration of 10\(^{-11}\) mol/l. The maximal stimulation of cortisol secretion was 928.1 ± 42.4 ng/10\(^3\) cells. Stimulation of cortisol secretion by angiotensin II was the same as in the normal collective.

Discussion

This paper describes the transition from pituitary-dependent to partially adrenal-dependent Cushing's syndrome in the natural course of the disease. In 1985, endocrinological tests (CRH test and dexamethasone suppression test) and imaging techniques (CT of the sella and adrenals) were indicative of pituitary-dependent Cushing's disease. Remarkable at that time, however, were the relatively low ACTH levels and the slight increase of ACTH in the CRH test. In 1990, on the other hand, ACTH was below the detection limit on four of six occasions and remained undetectable in the CRH test. Cortisol was not stimulated by CRH. In the dexamethasone suppression test, cortisol secretion and excretion in urine were suppressible, as observed in most patients with Cushing's disease. The fact that plasma ACTH was
Fig. 2. A. Chromophobe microadenoma of the pituitary (arrow), HE staining. B. Residual production of ACTH in the adenoma, immunohistological staining against ACTH by ABC method.
secretion in vitro was in the upper normal range compared with adrenocortical cells obtained from brain-dead organ donors (7). The development of nodular hyperplasia in Cushing’s disease is unclear. We and others postulate that some cases of pituitary Cushing’s disease initially exhibit a bilateral homogeneous adrenal hyperplasia which then develops into nodular hyperplasia; in the next stage of the disease single nodules may become autonomous and suppress ACTH secretion of the initially ACTH-secreting adenoma (6, 10). This hypothesis is supported by a number of cases of ACTH-dependent Cushing’s disease with unilateral nodular adrenal hyperplasia reported in the literature (2–5). Concerning the pathogenesis of bilateral micronodular adrenal hyperplasia, it is of interest that development of the pigmented micronodular adrenocortical disease may be due to long-lasting stimulation of the adrenal glands by circulating adrenal stimulating immunoglobulins (ASI) (8, 11, 12). In these patients plasma ACTH is undetectable or low and does not rise after iv injection of CRH. Plasma cortisol and urinary cortisol are unsuppressible even with high doses of dexamethasone. In our present patient, on the other hand, cortisol secretion was suppressed in the high dose dexamethasone test.

We feared the development of a complete adrenal-dependent Cushing’s syndrome. Therefore, bilateral adrenalectomy was performed. Development of pituitary tumors postadrenalectomy may occur in 7–20% of patients. Such patients usually have high plasma ACTH levels (13, 14).

Plasma ACTH in our patient was undetectable. Therefore the risk of Nelson’s syndrome in this elderly woman seemed to be low. In the case of Hermus et al. (6), with secondary “autonomization” of the adrenal glands transsphenoidal surgery was not successful. Only after removal of the left adrenal gland (with the macroadrenoma) and the right adrenal gland (containing micronodular hyperplasia) did the laboratory signs and clinical symptoms of Cushing’s syndrome disappear.

References
5. Lambers SWJ, Bons EG, Bruining HA. Different sensitivity to adrenocorticotropin of dispersed adrenocortical cells from patients with Cushing’s disease with macronodular and diffuse adrenal hyperplasia. J Clin Endocrinol Metab 1984:58:1106–10


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