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 micronodules 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 micronodules 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 micronodules 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 infract 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 darkening 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, GOT, 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-deoxy-cortisol 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
Table 1. Response of plasma ACTH and plasma cortisol to corticotropin-releasing hormone (1985 and 1990).

<table>
<thead>
<tr>
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<th>Minutes</th>
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<tbody>
<tr>
<td></td>
<td>15</td>
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<tr>
<td>ACTH 1985 (pmol/l)</td>
<td>2.62</td>
</tr>
<tr>
<td>ACTH 1990 (pmol/l)</td>
<td>&lt;1.65</td>
</tr>
<tr>
<td>Cortisol 1985 (nmol/l)</td>
<td>303</td>
</tr>
<tr>
<td>Cortisol 1990 (nmol/l)</td>
<td>471</td>
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At 11.00 (0 min) the patient received an intravenous bolus of 100 µg of h-CRH.

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 Cushings’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, LH>10 µg/l, LH<10 µg/l, LH<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 immunohistochemical 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 Cushings’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 Cushings’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
nmol respectively. The patient developed clinical signs of hypocortisolism. Treatment was discontinued, and short-term hydrocortisone replacement was needed.

**Morphology of the adrenal cortex**

The right adrenal weighed 11.5 g and was $55 \times 35 \times 25$ mm in size with sharply demarcated borders between the medulla and the partially micronodular (up to 7 mm) cortex, which was otherwise between 1 and 3 mm wide. The left adrenal weighed 12 g and was $65 \times 25 \times 20$ mm in size with many micronodules between 2 and 5 mm wide.

Microscopy revealed sections on both sides with micronodular hyperplasia in the zona fasciculata and multiple micronodular cortical prolapses: single lymphocytic infiltrates were also found (Fig. 1).

**Morphology of the pituitary**

The pituitary was found to contain a chromophobe microadenoma ($5 \times 7$ mm in size) with immunohistologically detected residual ACTH production. We had no evidence of LH, TSH, FSH, alpha-HCGH or prolactin 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 $123.5 \pm 8.6$ ng/10$^5$ cells (mean of four independent experiments ± SEM; normal: 23–225 ng/10$^5$ 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 $928.1 \pm 42.4$ ng/10$^5$ 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.
suppressed in 1990, despite the fact that the urinary cortisol excretion was lower than in 1985, indicates that suppression of the ACTH-producing pituitary adenoma occurred without progression of the hypercortisolism. A chromophobe microadenoma was found in the pituitary. ACTH was immunohistologically detectable in the adenoma cells. A bilateral micronodular adrenal hyperplasia was found in both adrenal cortices.

A case of Cushing’s disease with secondary “autonomization” of the adrenal gland was described by Hermus et al. in 1988 (6). ACTH was likewise undetectable and could not be stimulated in the CRH test. The dependence of cortisol secretion on pituitary ACTH was confirmed by the metyrapone and dexamethasone test. ACTH was clearly detectable after bilateral adrenalectomy. The histological examination showed a pituitary adenoma as well as a solitary macroadenoma of the left adrenal. Unlike our case, the long-lasting ACTH stimulation of the adrenals led to the formation of a semiautonomous macroadenoma. Here the autonomization of the adrenals was thus probably of mononodular origin. The patient we described, on the other hand, had multiple micronodules. What is special in our case, however, is the initial demonstration of a clearly pituitary-dependent Cushing’s syndrome in 1985 which in the course of five years underwent transition to partial autonomy of the adrenals with suppression of ACTH secretion. The suppression of ACTH secretion could be abolished by short-term ketoconazole therapy that led to low normal plasma and subnormal urine cortisol levels. A complete suppression of ACTH production, as in patients with cortisol-secreting adrenocortical adenomas, however, was not observed in our patient in 1990, as documented by cortisol suppression in the high dose dexamethasone test and occasional detection of low normal basal ACTH levels. The patient’s adrenal cells were sensitive to ACTH in vitro (Fig. 3). The maximal stimulated cortisol 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 macroadenoma) and the right adrenal gland (containing micronodular hyperplasia) did the laboratory signs and clinical symptoms of Cushing’s syndrome disappear.

References
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