Large bilateral adrenal incidentalomas complicating untreated 11β hydroxylase deficiency in the third decade of life

A case report

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The growing use of imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) has resulted in increasingly frequent discovery of adrenal incidentalomas [1].

In recent years, hormonal determinations of patients with incidentaloma demonstrated elevated basal 17 hydroxyprogesterone (17 OHP) in a large proportion of them [7], whether the enzymatic deficiency is intrinsic to the tumoral gland or may be attributed to the increased adrenal mass is still to be clarified [7].

On the other hand it has become evident that both homozygous and heterozygous patients with congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency, which is the most common type of enzymatic defect, have an increased prevalence of adrenal incidentaloma [3].

To our knowledge, there are no previous reports of the diagnosis of female pseudohermaphroditism caused by 11β hydroxylase made in the third decade of life in the course of evaluating adrenal incidentalomas. Here, we report the occurrence of giant bilateral adrenal incidentalomas in an untreated patient with CAH due to 11β hydroxylase deficiency.

We point out the potential for severe manifestations of the untreated...
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**CASE REPORT**

A 22-years-old male underwent a renal ultrasonography for a recurrant urinary tract infection. Bilateral adrenal masses were seen and later confirmed by CT. The right adrenal mass approximately 16 × 8 cm in size, was heterogeneous with posterior calcifications and evidence of hemorrhage. The left kidney was displaced inferiorly. The left adrenal gland measured 6 × 5 cm (fig. 1).

MRI of the abdomen confirmed the previous findings and suggested the possibility of bilateral corticosurrenalomas (fig. 2).

Our patient had no family history of clinically overt endocrine diseases. He is the youngest of eight children and is the product of a full term normal delivery.

The patient denied any symptoms referable to the masses, any history of repeated vomiting or hospitalizations as an infant or child.

He was not married and acknowledged no active sexual life. He developed a beard at age 4, began shaving at 6. He was one of the tallest members of his school class until about age 10 when he stopped growing in height.

The physical examination revealed an intelligent man with a height of 145 cm, a weight of 45 kg, and a blood pressure of 190/100 mmHg.

The external genitalia were completely masculinized, the penis was 6 cm in size with a first degree hypospadius (fig. 3).

Laboratory findings were as follows: hemoglobin: 11 g/dl; leukocyte count: 9 800/ml; platelet count: 250,000/ml; blood glucose level: 4.5 mmol/l; serum total protein: 72 g/l; blood creatinine: 103 umol/l. Serum electrolyte values were as follows: K+: 3.9 mmol/l, Na+: 140 mmol/l, Cl−: 99 mmol/l.

Urine electrolyte evaluation did not show any abnormalities.

Because of his short stature, detailed endocrinological measurements were performed (Table I).

Because no testis were palpable, a genitography was made and revealed a female internal duct (fig. 4).

A chromosome analysis showed a normal 46 XX female karyotype.

Fundoscopy was consistent with hypertensive retinopathy. A cerebral and hypothalamic pituitary MRI revealed paraventricular ischemic areas.

The patient received 30 mg hydrocortisone daily, resulting in urethral bleeding after 3 months of treatment. Nifedipine (adalate) 30 mg daily was then added because of persistent high blood pressure.
Figure 3: External genitalia.
Figure 3: Aspect des organes génitaux externes.

Figure 4: Genitography: lateral view shows: a female pseudohermaphroditism. B: bladder, u: uterus, s: urogenital sinus.
Figure 4: Génitographie vue de profil: pseudohermaphrodisme féminin.

Figure 5: Axial CT Scan obtained 6 months later shows a decrease in the size of the adrenal masses and appearance of calcifications (arrow).
Figure 5: Examen tomodensitométrique, 6 mois après traitement: nette diminution du volume des masses surrenaliennes, apparition de calcifications (flèche).

Table I
Endocrinological measurements in the plasma and their response to hydrocortisone treatment in our patient.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Response after IV ACTH at 60 mn</th>
<th>After treatment (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH RIA (n &lt; 48 ng/l)</td>
<td>1,402</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH IRMA (n: 1,5-7 mUI/ml)</td>
<td>0.5</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>LH IRMA (n: 1,1-11,7 mUI/ml)</td>
<td>1.3</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>Cortisol RIA (n: 75-220 ng/ml at 8 AM)</td>
<td>80</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Testosterone RIA (n: 0,1-0,7 ng/ml)</td>
<td>19</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>17 Hydroxyprogesterone RIA (n: 0,1-1,1 ng/ml)</td>
<td>&gt; 50</td>
<td>&gt; 50</td>
<td>5</td>
</tr>
<tr>
<td>11 Desoxycortisol RIA (n &lt; 30 nmol/l)</td>
<td>919</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHEA S RIA (n: 340-4 000 ng/ml)</td>
<td>3,120</td>
<td></td>
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</table>
After six months the patient underwent a new hormonal assessment (Table I) that showed a marked decrease of hormonal adrenal levels. Subsequently, a second CT scan showed a reduction in size of the left adrenal gland, the right one was about 4 cm (fig. 5).

**DISCUSSION**

Our patient raise several issues. These concern:

— the pathogenesis of adrenal incidentalomas in CAH;

— the diagnostic approach to adrenal incidentalomas in general and in patients with CAH in particular, and finally;

— the management of 11β hydroxylase deficiency diagnosed in later life.

Chronically elevated adrenocorticotropin (ACTH) levels may play a role in the pathogenesis of incidentalomas in CAH. Jaresch et al. [3] demonstrated that 83 % of patients homozygous for the simple virilizing form of the more common form of CAH which is caused by 21 hydroxylase deficiency have associated adrenal incidentalomas, and that even unmasked heterozygotes have a high incidence of 31 % [3].

Because 11β hydroxylase deficiency is less frequent and comprises only 5-8 % of cases of CAH [8], there is no available data regarding incidence of incidentalomas in this enzyme deficiency.

Our observation clearly demonstrates that chronic ACTH elevation, a characteristic of most CAH patients, plays a role in the development of adrenal masses in these patients.

It is the first documented case of spontaneous hemorrhage in a CAH that is due to the important tumor size. It is generally accepted that older patients and patients who were untreated for a long time have the most hyperplastic adrenals [3].

Second, endocrine evaluation of patients with adrenal incidentalomas by an ACTH test including 17 OHP before and after, is widely recommended unless the cause of the incidentiaoma is evident [1].

Thereafter, the evidence of a heterozygous 21 hydroxylase deficiency, as indicated by the exaggerated (17 OHP) response after ACTH, has been widely reported [1].

However, obligate heterozygous carriers of 11β hydroxylase deficiency allele have no consistent biochemical abnormalities detectable even after stimulation of the adrenal cortex with IV ACTH [5].

As a practical consequence, the presence of enzymatic defects in patients with incidentalomas is of clinical importance.

Although glucocorticoid treatment caused a marked shrinkage of the adrenal tumors in our patient, it appears reasonable to follow such patients with incidentalomas both clinically and with periodic CT scan: the opportunity of a surgical approach is to be considered, because adrenal carcinomas may occur in patients with CAH even if it has been described in only four cases [2, 4].

Finally, our patient highlights the problem of the treatment of unusual patients presenting in later life as female pseudohermaphrodites. Routine glucocorticoid therapy may produce menstrual bleeding, as our patient demonstrated. This new event may cause severe psychological disturbance [6].

However, lifetime glucocorticoid replacement must absolutely be considered in our patient because of his long-standing hypertension. Adjunctive drugs may be required as in our patient and calcium channel blockers had proven to be effective in the treatment of hypertension in CAH by 11β hydroxylase deficiency [8].

**CONCLUSION**

Untreated patients with CAH may present in later life with bilateral adrenal masses. Our case clearly demonstrates that the adrenal tumors are under control of a chronic ACTH elevation, and that glucocorticoid treatment allows reduction in size of even giant adrenal masses.

**REFERENCES**