CASE REPORT

Bilateral testicular enlargement due to adrenal remnant in a patient with C11 hydroxylase deficiency congenital adrenal hyperplasia

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ABSTRACT. The case of a 15-yr-old boy with C11 hydroxylase deficiency congenital adrenal hyperplasia is reported who was diagnosed and treated as true precocious puberty at the age of 2 yr because of virilization and bilateral testicular enlargement. He later developed hyperpigmentation, hypertension and short stature and because of an increase in testes size he underwent testicular biopsy with the assumption of Leydig cell tumor. With the intake of glucocorticoids his testes size, hypertension and hyperpigmentation improved markedly. We could find only 6 such cases in the literature and have reviewed their clinical and laboratory data. All patients showed the picture of virilization with hypertension. Leydig cell tumor was proposed as the differential diagnosis in all cases except ours. Ultrasonography was able to show testicular adrenal-like tissue in all those in whom the procedure was undertaken. In the 5 patients of whom we could find enough data, 1 responded partially and 4 responded markedly to corticosteroid therapy with shrinkage of testicular tumors. We conclude that clinical findings and US are very important in the early diagnosis of these patients and with adequate treatment most cases show shrinkage in testicular tumors. (J. Endocrinol. Invest. 26: 84-87, 2003)

INTRODUCTION

Testicular enlargement due to the overgrowth of adrenal remnant tissue in C11 hydroxylase deficiency (C11 HD) congenital adrenal hyperplasia (CAH) is very rare. To the best of our knowledge only 6 cases have been reported in the literature (1-5). The enlarged firm testes, which are almost always due to non-compliance with treatment may be mis-interpreted as Leydig cell tumor and, while the histologic differentiation is not always easy, unnecessary orchectomy may be undertaken. We here present a new case with review of the clinical and laboratory data of the 6 previously reported cases. In the present case, enlargement of the testes led to the diagnosis of true precocious puberty and postponed the logical treatment of the patient.

PRESENTATION OF THE CASE

A 15-yr-old boy was referred to the Department of Endocrinology and Metabolism at the Taleghani Teaching Hospital, Tehran, Iran, for the evaluation of short stature, hypertension and sexual precocity. The patient’s problem had begun at the age of 2 yr, when his parents noted polyphagia, abnormally high growth rate, increase in penile size and growth of pubic hair. The information in the patient’s file revealed the following: height 129 cm (>97 percentile), weight 30 kg (>97 percentile), increased penile size and bilateral testicular enlargement. FSH was 1 mIU/ml (normal values <3), LH was 8 mIU/ml (normal values <3), PRL was 15 ng/ml (normal values <15) and T was 450 ng/dl (normal values 5-20). Bone age was 11 yr and pituitary CT scan was reported as normal. The case was diagnosed as true precocious puberty and treatment was begun with medroxyprogesterone, 100 mg im injection every 2 weeks. The patient discontinued the medication after a short period and did not seek medical attention until the age of 11 yr, when he developed recurrent attacks

Key-words: Adrenal rest tumor, C11 hydroxylase, congenital adrenal hyperplasia, bilateral testicular enlargement, precocious puberty.

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of headache, nausea, vomiting and dyspnea. His BP was found to be in the range of 180/110 to 200/120 mmHg and the patient was treated with nifedipine, enalapril, triameterene and prazosin in different combinations and incremental dosages. There was no history of a similar disease in any member of the family: In fact, one brother and one sister were reported to be normal, father and mother of the patient were cousins. Our evaluation revealed a completely masculinized, hyperpigmented young muscular man. Body weight 51 kg, height 145 cm, BP 160/130 mmHg. He had facial acne, normal thyroid and arterious-venous nicking on fundoscopic examination. ECG and chest X-ray revealed left ventricular hypertrophy. Renal US findings were right kidney 94 and left kidney 90 mm with thinning of the cortices and medullary nephrosclerosis. Penis was normally sized and both testes were irregular and hard on palpation with a volume of more than 25 ml each.

US and color doppler study of the testes showed bilateral enlarged tested with heterogenous echo accompanied by increased blood flow. Bilateral testicular tumors were suggested. diethylenetriaminepentaacetic acid (DTPA) renal scan was normal. Routine laboratory evaluation including BUN, creatinine and thyroid function test were normal: LH 0.5 mIU/ml (normal values: 1-18), FSH 0.3 mIU/ml (normal values: 1-17), F 14 µg/dl, (normal values: 8-24), T 2050 ng/dl (normal values:300-1200), DHEAS 1000 mg/dl (normal values:130-400), and 17-OHP 19.2 ng/ml (normal values:1.5-2.4).

The patient underwent a bilateral testicular biopsy which disclosed pieces of neoformed tissue composed of cells with eosinophilic cytoplasm, elliptical nuclei and round nucleoli. There was no mitotic activity. The cells were lined in sheets and were separated by fibrous bands. No crystalloids of Reineke were present.

Treatment with dexamethasone was started with 1 mg/day at bedtime. After 1 yr, the patient’s hyperpigmentation was markedly reduced, blood pressure was 110/80 mmHg, testicular volume decreased to 12 ml each and there was marked reduction in testicular nodularity. Laboratory evaluation revealed, DHEAS <5 mg/dl, T 20 ng/dl and 17 OHP 0.2 ng/ml.

**DISCUSSION**

While testicular enlargement due to adrenal rest tumors in patients with C21 hydroxylase deficiency (C21 HD) has been well defined (6), reports of this complication in patients with C11 HD are very rare. This rarity is in part due to the fact that C11 HD is the cause of CAH in only 5-8% of the patients (7). C11 HD is much more prevalent in Asian, African Jews and Iranians (8). We have no data on the ethnic origin in 4 patients but it is interesting to note that the 3 reported cases were from Iran, Turkey and Israel.

Inherited as an autosomal recessive disease, deficiency in 11 hydroxylase activity decrease the conversion of 11 deoxycortisol to F in the glucocorticoid pathway, 11 deoxycorticosterone to corticosterone and aldosterone in the mineralocorticoid pathway. Deficiency in the synthesis of F is the stimulus for hypersecretion of ACTH, which results in adrenal gland hyperplasia with overproduction of intermediary substances, which lead to a clinical syndrome of rapid growth, virilization and hypertension.

Bilateral testicular enlargement in these patients has been attributed to overgrowth of adrenal remnant cells under the influence of ACTH. Ectopic adrenal tissue has been reported in different anatomic sites. These cells, which probably originate from pleuripotential cells of the urogenital

<table>
<thead>
<tr>
<th>Author</th>
<th>Age at diagnosis</th>
<th>Age at presenting with enlarged testes</th>
<th>Testes size</th>
<th>Palpation Shape</th>
<th>Palpation Firmness</th>
<th>US findings</th>
<th>Response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bricaire (1)</td>
<td>17</td>
<td>4</td>
<td>Enlarged</td>
<td>Irregular</td>
<td>Hard</td>
<td>ND</td>
<td>Marked</td>
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<tr>
<td>Willi (2)</td>
<td>12</td>
<td>2</td>
<td>9 ml</td>
<td>Normal</td>
<td>Normal</td>
<td>TALT+</td>
<td>ND</td>
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<tr>
<td>Willi (2)</td>
<td>19</td>
<td>5</td>
<td>11 ml</td>
<td>Irregular</td>
<td>Hard</td>
<td>TALT+</td>
<td>Partial</td>
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<tr>
<td>Srikant (3)</td>
<td>13</td>
<td>3</td>
<td>ND</td>
<td>Irregular</td>
<td>Hard</td>
<td>ND</td>
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<td>Ober can (4)</td>
<td>13</td>
<td>13</td>
<td>R=10x4x4cm</td>
<td>Irregular</td>
<td>Hard</td>
<td>ND</td>
<td>Marked</td>
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<tr>
<td>Karnak (5)</td>
<td>17</td>
<td>2</td>
<td>7.5x4x4cm</td>
<td>Irregular</td>
<td>Hard</td>
<td>TALT+</td>
<td>Marked</td>
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</tbody>
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L: left; ND: not determined; R: right; US: ultrasound; TALT: testicular adrenal-like tissue.

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Table 1—Clinical and ultrasonographic findings in 7 patients with 11 hydroxylase deficiency and bilateral testicular enlargement.