Sporadic Testotoxicosis in Japanese Children: Report of 4 Cases

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Abstract. Familial testotoxicosis is a gonadotropin-independent autosomal dominant condition in which precocious puberty occurs, only in males. We present the cases of four Japanese boys with precocious sexual development aged 3 to 4 years, who showed pubertal serum testosterone levels, but with low basal serum gonadotropin levels and a minimal response of gonadotropins to luteinizing hormone releasing hormone. They showed symmetric testicular enlargement, premature Leydig cell maturation and spermatogenesis. There was no evidence of familial sexual precocity in three generations. These findings are consistent with familial testotoxicosis except for the negative family history. In a nationwide survey for precocious puberty in Japan, there were no familial cases of male-limited sexual precocity. It appears that this disease is limited to sporadic cases and is very rare in Japan.

Key words: precocious puberty, familial testotoxicosis, gonadotropin-independent precocious puberty

Abbreviations used; LH: luteinizing hormone, FSH: follicle stimulating hormone, LHRH: LH releasing hormone, HCG: human chorionic gonadotropin

Familial testotoxicosis or gonadotropin-independent sexual precocity is a disease characterized by premature Leydig and germinal cell maturation in the absence of pituitary gonadotropin stimulation. Endocrine features of this unusual form of precocious puberty include low basal levels of immuno-reactive and bioactive serum luteinizing hormone (LH), low LH and follicle stimulating hormone (FSH) response to LH releasing hormone (LHRH), and absence of the pubertal pattern of pulsatile LH secretion [1,2,3,4]. The familial occurrence of the disease has been repeatedly stressed, but a positive family history is not always obtained. In the Japanese population the first case of testotoxicosis was reported in 1987, and there was no family history of precocious puberty [5]. Since then three more cases have been found in Japan, also without a family history of the
disease. In this report all the above cases are reviewed.

**Case Reports**

**Patient 1.** He was a Japanese boy, delivered normally after an uncomplicated pregnancy. Birth weight was 3,780 g. His postnatal development was unremarkable until 2 years of age when he started to grow rapidly, with signs of puberty at the age of 3. The family history over three generations was negative for early sexual maturation. When first seen at 4.5 years of age, he was 128 cm tall (±5.8 SD for age). Bone age was 10.5 years. The patient showed a muscular body build, and had a deep voice and facial acne. He was classified as Tanner stages G3 and PH2. Testicular biopsy revealed spermatids, spermatozoa and aggregates of Leydig cells. Pneumoencephalography showed no evidence of brain tumor. Treatment was given with medroxyprogesterone acetate until age 7.5 years, when his bone age was 15.5 years. He reached a final height of 160 cm at age 10 years (Fig. 1) and was fully virilized by 15 years of age. The patient is now a medical student.

**Patient 2.** This Japanese boy was born after 34 weeks gestation. He weighed 1,720 g and his length was 42 cm. The pregnancy had been complicated by toxemia. His initial weight gain was poor. The family history over three generations was negative for early sexual maturation. His growth was poor during infancy and the weight and length at 9 months of age were recorded as 5.8 kg and 65 cm, respectively. Although no data on physical growth were available, the parents noticed that he grew rapidly, and had rapid penile enlargement, pubic hair and deepening of the voice by age 4 years 6 months. When aged 6 years 8 months, examination showed height 125.6 cm (±1.7 SD for age), weight 24.6 kg, and Tanner stages G3 and PH3. Bone age was 10.5 years. The testicular volume was 10 ml bilaterally, and the penile length was 7 cm. Testicular biopsy revealed active spermatogenesis and aggregates of Leydig cells. Nocturnal emissions were also noticed. There were no abnormalities on brain CT scan and magnetic resonance imaging. For the next 1 year 7 months the patient was

**Patient 3.** He was a 5 years 3 months old Japanese boy presenting with rapid growth, penile enlargement and pubic hair since 2 years previously. He weighed 3,180 g at birth. The pregnancy had been without complications. There was no family history of sexual precocity. On examination his height was 127.7 cm (±4.6 SD for age), weight 26.7 kg, and Tanner stages G3 and PH3. Bone age was 10.5 years. The testicular volume was 10 ml bilaterally, and the penile length was 7 cm. Testicular biopsy revealed active spermatogenesis and aggregates of Leydig cells. Nocturnal emissions were also noticed. There were no abnormalities on brain CT scan and magnetic resonance imaging. For the next 1 year 7 months the patient was

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Fig 1. Growth curve of the patients. Arrows indicate the time of first attendance.
treated consecutively with cyproterone acetate, medroxyprogesterone acetate, and LHRH analogue (Sprecur, Hoechst), but unsatisfactorily. At present he is 6 years 10 months and 141.0 cm tall (+4.6 SD for age). There were no changes in height SD score during this period (Fig. 1).

Patient 4. This patient was a 5 years 6 months old Japanese boy presenting with rapid growth and pubic hair. He weighed 2,584 g at birth. The pregnancy was uncomplicated. There was no family history of sexual precocity. His height was described as 97.3 cm at age 3 years 1 months (+0.67 SD for age) and 108.0 cm at age 4 years (+2.05 SD for age). On examination his height was 123.0 cm (+2.97 SD for age), weight 22.5 kg, and Tanner stages G3 and PH2. The testicular size was 27×16 mm bilaterally, and the penile length was 5.5 cm. Testicular biopsy revealed active spermatogenesis and scattered foci of Leydig cells. There were no abnormalities on brain CT scan and magnetic resonance imaging. Subsequently, the patient was treated with cyproterone acetate. Two years later the testicular size and pubic hair remained unchanged.

Methods

Endocrine studies were carried out at the Department of Pediatrics at Asahikawa Medical College, Asahikawa (patients 1 and 2), at Kawasaki Medical College, Kurashiki (patient 3) and at Yamagata University, Yamagata (patient 4). Informed consent was obtained from the parents for all studies. Serum testosterone and dehydroandrosterone sulfate (DHEA-S) were measured by radioimmunoassay (RIA). Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured by double antibody radioimmunoassay using the 2nd International Reference Preparation of Human Menopausal Gonadotropin (2nd IRP-HMG) as a standard for Patient 1, and by immunoradiometric assay (IRMA) using Spac-S kits (Daiichi Radioisotope Institute, Tokyo) for Patients 2, 3 and 4. In the IRMA, the 1st IRP LH (68/

Table 1. Clinical summary and hormonal data

<table>
<thead>
<tr>
<th></th>
<th>patient 1</th>
<th>patient 2</th>
<th>patient 3</th>
<th>patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (yr)</td>
<td>&lt;3</td>
<td>4·1/2</td>
<td>&lt;3</td>
<td>3·2/12</td>
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<tr>
<td>Age of 1st examination (yr)</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>6</td>
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<tr>
<td>Familial occurrence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Leydig cell hyperplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Spermatogenesis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH (mU/ml)*</td>
<td>&lt;1.0</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
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<tr>
<td>Basal level</td>
<td>&lt;1.8</td>
<td>&lt;0.5</td>
<td>1.5</td>
<td>4.8</td>
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<tr>
<td>Peak after LHRH</td>
<td>1.8</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>FSH (mU/ml)*</td>
<td>3.0</td>
<td>&lt;0.5</td>
<td>3.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Basal level</td>
<td>3.0</td>
<td>&lt;0.5</td>
<td>3.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Peak after LHRH</td>
<td>&lt;2.0</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>HCG (mU/ml)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal level</td>
<td>1.12</td>
<td>2.09</td>
<td>2.04</td>
<td>1.75</td>
</tr>
<tr>
<td>Peak after HCG</td>
<td>not done</td>
<td>11.47</td>
<td>13.80</td>
<td>not done</td>
</tr>
<tr>
<td>DHEA-S (ng/ml)</td>
<td>not done</td>
<td>135</td>
<td>311</td>
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Urine

<table>
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<th>patient 2</th>
<th>patient 3</th>
<th>patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-OHCS (mg/day)</td>
<td>3.8</td>
<td>2.7</td>
<td>5.0</td>
<td>2.4</td>
</tr>
<tr>
<td>17-KS (mg/day)</td>
<td>3.6</td>
<td>1.3</td>
<td>2.7</td>
<td>0.65</td>
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</tbody>
</table>

*LH and FSH in Patient 1 were measured by double antibody RIA method and in Patients 2, 3 and 4 they were measured by IRMA.
**HCG in Patient 1 was measured by double antibody method and in Patients 2, 3 and 4 it was measured by TR-FIA.
Fig 2. LH and FSH responses to the LHRH test. Shaded areas indicate normal range for boys at Tanner stage G2 puberty. All the patients showed no or low responses to the LHRH test. In Patient 1 (left panel) 2nd IRP-HMG was used as a standard for the LH and FSH assay. In Patients 2, 3 and 4 (right panel) 1st IRP LH (68/40) and 2nd IRP FSH/LH (78/549) were used as standards for LH and FSH assay, respectively.

40) and the 2nd IRP FSH/LH (78/549) were used as standards for LH and FSH, respectively. Serum LH and FSH levels measured by the above RIA method were approximately 5 times and 2 times higher than by the IRMA method, respectively. The LHRH test was performed by a single iv injection of LHRH (2 μg/kg) and blood samples for LH and FSH assay were obtained before and 15, 30, 60, 90 and 120 minutes after the injection. Serum human chorionic gonadotropin (HCG) was measured by double antibody RIA in Patient 1 and by time resolved fluorescent immunoassay using Delfia HCG kits (Pharmacia Japan, Tokyo) in Patients 2, 3 and 4. The bioactivity of LH was measured by in vitro testosterone production using porcine Leydig cells [6]. The testosterone response to HCG was evaluated after 3 daily doses of 2000 U of HCG.

Results

Basal levels of serum testosterone in all the patients ranged from 1.12 to 2.09 ng/ml, which corresponded to mid-pubertal levels, while the serum LH and FSH values remained prepubertal and the serum HCG levels were lower than the detectable limits (table 1). An LHRH test was performed on three occasions in Patient 1. He showed no response at age 4 years 6 months and a low response at ages 8 years 6 months and 10 years 5 months (Fig 2. left). Patients 2, 3 and 4 showed no or low responses to LHRH (Fig 2. right). The HCG test was performed in Patients 2 and 3 and showed a good response of testosterone. Urinary 17-OHCS were normal for age. Urinary 17-KS were also normal for age but low for the pubertal stage. The serum bioactive LH in Patient 1 was only one fourth of that in normal mid-pubertal boys (table 2). The serum DHEA-S in Patients 2 and 3 was appropriate for their ages.

Discussion

The clinical features and hormonal findings in our patients were consistent with familial testotoxicosis or gonadotropin-independent
Non-familial Testotoxicosis

Table 2. Bioactive LH assayed by testosterone production using porcine Leydig cells

<table>
<thead>
<tr>
<th>Age</th>
<th>Pubertal stage</th>
<th>i-LH • by RIA (mU/ml)</th>
<th>b-LH • (ng/ml)</th>
</tr>
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<tr>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control: A</td>
<td>12</td>
<td>G3, PH2</td>
<td>27</td>
</tr>
<tr>
<td>B</td>
<td>12</td>
<td>G3, PH2</td>
<td>39</td>
</tr>
<tr>
<td>Patient 1</td>
<td>17</td>
<td>G5, PH5</td>
<td>7.1</td>
</tr>
</tbody>
</table>

*: i-LH; immunoreactive LH, b-LH; bioactive LH

familial sexual precocity except for the absence of familial occurrence.

It has been reported that serum from patients with familial testotoxicosis does not stimulate testosterone secretion from rat Leydig cells [1,4]. A similar result was obtained in Patient 1 in our study using porcine Leydig cells. The low serum levels of both immunoreactive and bioactive LH are characteristic in patients with familial testotoxicosis. The normal testosterone response to HCG stimulation observed in our patients and by others [1] indicates that the HCG and LH sensitivity of the Leydig cells is normal in patients with this disease. It suggests that the cause of this disease is an intragonadal regulatory disorder of testosterone production [1,2,4,7]. On the other hand, Holland et al. [8] showed elevated levels of bioactive LH in this disease by mouse Leydig cell bioassay and rat ovarian membrane radioreceptor assay. A recent study by Manasco et al. [9] demonstrated a circulating testis-stimulating factor in the plasma of boys with familial testotoxicosis using adult cynomolgus monkeys. It is difficult to explain this conflicting evidence.

A Japanese nationwide survey for precocious puberty was made during 1973-75 [10]. In this survey, the diagnosis of precocious puberty was made on the basis of premature appearance of secondary sex characteristics and accelerated bone age. Patients with familial testotoxicosis, if any, would have been included. But no familial cases were found in the 144 patients with precocious puberty. The next survey was made in 1984 and again there were no familial cases except for two female patients out of 272 patients [11]. During the past 15 years the LHRH test has been widely used as a diagnostic test for precocious puberty. Because of the low or absent response to LHRH in familial testotoxicosis, it is easy to differentiate from central precocious puberty. To the best of our knowledge there were only the 4 patients with the disease described above and none had a family history of precocious puberty. This indicates that the disease is limited to sporadic cases and is extremely rare in the Japanese population.

The low incidence of the disease might be explained by low genetic penetrance. It has been pointed out that familial testotoxicosis can be transmitted through several generations of non-affected carrier females and that individual patients may be encountered in whom a positive familial history cannot be established [2]. Another possible explanation is the poor fertility of the patients.

Acknowledgments

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