46, XY Pure Gonadal Dysgenesis: A Case with Graves’ Disease and Exceptionally Tall Stature


Abstract

A case of 46, XY pure gonadal dysgenesis with very tall stature was investigated. The 24-year-old, phenotypically female patient consulted our clinic because of linear growth persisting into adulthood. The patient was found to have no mutation or deletion of a sex-determining region of the Y chromosome, and also was found to have Graves’ disease. Growth was arrested with height remaining at 187 cm after normalization of the thyroid function by treatment with an antithyroid agent, although follow-up to monitor growth was limited to 3 months. In some cases of gonadal dysgenesis, then, Graves’ disease may contribute to an abnormally tall stature. (Internal Medicine 40: 740-743, 2001)

Key words: XY female, hyperthyroidism, sex-determining region of the Y chromosome, streak gonad

Introduction

Pure gonadal dysgenesis (Swyer-James syndrome) is a variety of defective organogenesis in which phenotypically female patients with a 46,XY karyotype completely lack functioning gonadal tissue but show normal female external genitalia (1). Mutations in the genes of the sex-determining region of the Y chromosome (SRY) represent one cause of the syndrome, but such mutations account for only 15 to 25% of cases (2); thus, the pathogenesis of 46,XY pure gonadal dysgenesis in most cases, has yet to be determined. The stature of patients with this dysgenesis ranges from normal to tall, though with heights remaining within 2 standard deviations of the growth curve. We report a patient with 46,XY pure gonadal dysgenesis who had extremely tall stature and Graves’ disease. We discuss the etiology of the very tall stature in this patient.

Case presentation

A 24-year-old female patient was referred to our clinic on June 6, 1999 for the investigation of tall stature and primary amenorrhea. At birth, her height was normal (50 cm), and height remained approximately average for a Japanese girl until the age of 12 years. Since then, the growth rate exceeded the average, and growth continued to adulthood (Fig. 1). She complained of no symptoms of Graves’ disease.

Family history

The family history included no consanguinity. Although the heights of the patient’s father (173 cm) and mother (158 cm) were normal, two sisters, aged 21 and 19 years were tall (175 cm) and had primary amenorrhea. They had no brother. The patient worked at an office; her older sister was a hospital nurse and her younger sister was a college student. No one in the family including the patient had a history of mental or emotional problems. No very tall stature, primary amenorrhea, or delayed sexual development was present except in the patient and her sisters.

Physical examination

Physical examination revealed a height of 187.1 cm, an arm span of 193.5 cm of arm span, and an upper body segment height of 87.4 cm. Weight was 57.2 kg. Sex characteristics included poorly developed breasts (Tanner stage I), sparse pubic hair (Tanner stage II), and normal female external genitalia with no clitoral enlargement; the vagina and cervix were normal. The stigmata of the Turner syndrome phenotype were not present. The thyroid gland was diffusely enlarged. The patient showed a hand tremor but lacked exophthalmos. No other abnormal physical findings were noted.

Laboratory investigations

In routine examinations of urine and blood, no abnormality was detected except for an elevation of serum alkaline phos-
Gonadal Dysgenesis with Graves' Disease

Endocrinologic findings (Table 1) included those of hypergonadotropic hypogonadism and those of hyperthyroidism by elevated free triiodothyronine and free thyroxine, decreased thyroid stimulating hormone (TSH), and high titers of autoantibodies against thyroid peroxidase, activity, thyroglobulin, and the TSH receptor. No testosterone response occurred to four daily injections of human chorionic gonadotropin (Fig. 2). Estradiol was undetectable in serum before and after intramuscular injections of human menopausal gonadotropin (50 IU per day) for 4 consecutive days. The limit of detectability was 10 pg/ml.

Imaging studies

Radiographs of the left hand showed the bones skeleton to be osteopenic with a bone age of approximately 14 years (3); (Fig. 3). Magnetic resonance imaging (MRI) of the abdomen and pelvis indicated that the uterus was atrophic and flat, while no ovarian or testicular structures were detected except for bilateral patchy or streak-like structures showing signals of soft tissue density between the internal iliac arteries. Iodine-123 was used for thyroid imaging and determination of uptake by the gland. The thyroid gland was shown to be diffusely enlarged, and the iodine uptake was homogenous throughout the gland. Percent uptake was 53.5% 24 hours after injection of the isotope (normal range, 10 to 40%).

Table 1. Baseline Data for Serum Hormones and Autoantibodies on Admission

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH, IU/l</td>
<td>17.2</td>
<td>(1.8–5.2)</td>
<td>(1.8–7.6)</td>
</tr>
<tr>
<td>FSH, IU/l</td>
<td>56.1</td>
<td>(2.9–8.2)</td>
<td>(5.2–14.4)</td>
</tr>
<tr>
<td>Prolactin, ng/ml</td>
<td>8.7</td>
<td>(1.5–9.7)</td>
<td>(1.4–14.6)</td>
</tr>
<tr>
<td>ACTH, pg/ml</td>
<td>32</td>
<td>(9–52)</td>
<td>(9–52)</td>
</tr>
<tr>
<td>TSH, IU/l</td>
<td>&lt;0.01</td>
<td>(0.34–3.5)</td>
<td>(0.34–3.5)</td>
</tr>
<tr>
<td>Free triiodothyronine, pg/ml</td>
<td>8.01</td>
<td>(2.47–4.34)</td>
<td>(2.47–4.34)</td>
</tr>
<tr>
<td>Free thyroxine, ng/dl</td>
<td>3.36</td>
<td>(0.97–1.79)</td>
<td>(0.97–1.79)</td>
</tr>
<tr>
<td>TgAb, IU/ml</td>
<td>10,552</td>
<td>(&lt;70)</td>
<td>(&lt;70)</td>
</tr>
<tr>
<td>TPOAb, IU/ml</td>
<td>608</td>
<td>(&lt;18)</td>
<td>(&lt;18)</td>
</tr>
<tr>
<td>TSHRAb, %</td>
<td>15</td>
<td>(&lt;15)</td>
<td>(&lt;15)</td>
</tr>
<tr>
<td>Growth hormone, ng/ml</td>
<td>0.30</td>
<td>(&lt;0.42)</td>
<td>(0.66–3.68)</td>
</tr>
<tr>
<td>IGF-I, ng/ml</td>
<td>250</td>
<td>(85–369)</td>
<td>(119–389)</td>
</tr>
<tr>
<td>Cortisol, ug/dl</td>
<td>8.0</td>
<td>(4.0–18.3)</td>
<td>(4.0–18.3)</td>
</tr>
<tr>
<td>Aldosterone, pg/ml</td>
<td>72</td>
<td>(30–159)</td>
<td>(30–159)</td>
</tr>
<tr>
<td>DHEA-S, ng/ml</td>
<td>2,340</td>
<td>(1,650–5,420)</td>
<td>(850–2,990)</td>
</tr>
<tr>
<td>Estradiol, pg/ml</td>
<td>&lt;10</td>
<td>(20–59)</td>
<td>(11–82)</td>
</tr>
<tr>
<td>Progesterone, ng/ml</td>
<td>0.7</td>
<td>(&lt;0.7)</td>
<td>(&lt;1.7)</td>
</tr>
<tr>
<td>Testosterone, ng/dl</td>
<td>14</td>
<td>(250–1100)</td>
<td>(10–60)</td>
</tr>
</tbody>
</table>

The normal range in women represents values for the follicular phase. LH: luteinizing hormone, FSH: follicle-stimulating hormone, ACTH: adrenocorticotrophic hormone, TSH: thyroid-stimulating hormone, TgAb: autoantibody to thyroglobulin, TPOAb: autoantibody to thyroid peroxidase, TSHRAb: autoantibody to TSH receptor, IGF-I: insulin-like growth factor I, DHEA-S: dehydroepiandrosterone sulfate.
Before injection

![Figure 2. Serum concentrations of testosterone before and after intramuscular injections of human chorionic gonadotropin for 4 consecutive days. Each injection was performed at 8 AM and blood was sampled shortly before injection. Arrows indicate injections of 5,000 IU per day of human chorionic gonadotropin.]

Chromosomal and DNA analyses

Chromosomes from peripheral lymphocytes were studied by conventional bandings (SRL Laboratories, Tokyo), which demonstrated a karyotype of 46,XY and no evidence of mosaicism. Informed consent of DNA analysis was obtained from the patient and her parents. Primers for polymerase chain reaction (PCR) method were selected in SRY region to flank the entire coding region including HMG box [an upstream primer 5’-GGCACCTTTCAATTTTGTCG-3’ (nucleotide number 371-390) and a downstream primer 5’-AGGTAGGTCTTTGTAGCAAA-3’ (nucleotide number 1,040-1,031)] according to published SRY sequence (4, 5). PCR and direct sequence of PCR products were performed using Dye Terminator Amplitaq FS kit (Applied Biosystem, Los Angeles, CA, USA) and analyzed by an ABI373A automated sequencer (Applied Biosystem) as described previously (6). The SRY gene showed a 100% nucleotide sequence identity with the reported cloned sequence of the normal gene (5). The protocol was approved by the institutional review board of Hokkaido University.

Diagnosis and clinical course

Considering all findings as a whole, the patient was diagnosed with 46,XY pure gonadal dysgenesis with an intact SRY gene and also was diagnosed with Graves’ disease. On July 9 we initiated oral administration of 300 mg of propylthiouracil to treat Graves’ disease. After thyroid function had normalized, laparoscopy was performed on August 19. This examination failed to macroscopically detect any streak gonads in the pelvis. Since the MRI had suggested streak-like tissues, and because 55% of patients with 46,XY pure gonadal dysgenesis had been reported to harbor or develop gonadal neoplasms (7), tissues around the internal iliac arteries were dissected. Pathologic examination showed only adipose tissue and fallopian tubes. After discharge on September 19, the patient continued to take oral propylthiouracil, and the thyroid function remained normal. Three months after normalization of thyroid function, the patient’s height was 187.2 cm, while the projected height in the absence of intervention estimated from her growth curve would have been 188.0 cm. Her bone age remained at 14 years-old. Then, oral administration of conjugated estrogen (Premarin) was initiated.

Discussion

A Medline search for articles published in English or Japanese from 1990 to 1999 disclosed 9 reports of 11 patients over 15 years old with Swyer syndrome. Mean height was 164 cm (range from 145 cm to 186 cm), indicating that our patient had a very tall stature compared with other patients. On her growth curve, the growth rate became abnormal at puberty. To our knowledge, this is the first report where pure gonadal dysgenesis was complicated by Graves’ disease. Abnormal growth in this patient may partly have resulted from this combination of endocrine disorders. Thyroid hormone is known to have a permissive role in pubertal growth (8). Wong et al (9) observed that 105 Chinese patients under 15 years old with hyperthyroidism were relatively tall compared with sex- and age-matched Chinese control subjects. High concentrations of thyroid hormone in the presence of hypogonadism are believed to have induced ongoing growth in the present case. Thyroid
hormone stimulates growth not only by a direct effect on cartilage, but also by an effect on secretion of growth hormone (8). However, the concentrations of growth hormone and insulin-like growth factor I were normal in our patient.

Growth was suppressed, after the patient’s thyroid function was normalized, since the actual height began to fall short of projected height in the absence of intervention. Although the difference was small (0.8 cm), error of measurement by nursing staff was not likely to be responsible. When the patient was admitted, the possibility of such error was evaluated, with the maximum difference between height measurements made by 14 nursing staff members being only 0.3 cm. The patient’s height was measured every 2 weeks following admission. These observations support the view that the abnormal growth in this patient may have resulted in part from the added presence of Graves’ disease.

Skeletal immaturity also is likely to have contributed to the tall stature in our patient. Estrogen is a potent factor in epiphyseal closure (8, 10, 11), and the estrogen concentration was lower than that seen in normal men. As the dehydroepiandrosterone sulfate concentration was normal, the patient may have absent or low activity of aromatase (11, 12), which converts adrenal androgen to estrogen. However, aromatase activity was not measured in our patient.

Chromosomal analyses of the patient’s sisters also revealed a karyotype of 46,XY (not illustrated), and they had physical characteristics similar to those of the patient, indicating that gonadal dysgenesis had occurred as a familial cluster. Uniquely in the present patient, streak gonads were undetectable, even after laparoscopic and pathologic examination. Pathologic features of streak gonads depend on the presence or absence of SRY mutations (13), suggesting that abnormal gonadal structure reflects different forms of abnormality of the sex differentiation cascade (14). Undetectable streak gonads may represent a specific form of abnormal differentiation involving growth-related factors (15).

In conclusion, we presented a patient with 46,XY pure gonadal dysgenesis including the atypical characteristics of very tall stature and undetectable streak gonads. Graves’ disease appears to be a factor in the tall stature in this case.

References