Central Precocious Puberty in 48,XXYY Klinefelter Syndrome Variant

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ABSTRACT

We report the first case of central precocious puberty in a patient with 48,XXYY Klinefelter syndrome variant. We also report clinical characteristics, growth pattern, endocrine data and pathological testicular findings. The patient did not receive medical care for his precocious pubertal development, because of adequate height prognosis, and reached normal height for both his target height and Klinefelter patients. Since precocious puberty seems to occur in Klinefelter syndrome and its variants, we advise karyotype analysis in boys with mental retardation, gynecomastia, small testes and precocious onset of puberty.

KEY WORDS

48,XXYY Klinefelter syndrome variant, central precocious puberty, growth, testicular biopsy

INTRODUCTION

Klinefelter syndrome (47,XXY) and its variants are the commonest cause of pubertal delay and primary hypogonadism in males.¹² Patients with the 48,XXYY karyotype constitute about 3% of chromatin-positive males; the incidence of this variant is estimated to be one in 50,000 male births.³ Usually, these patients show severe primary hypogonadism, poorly developed secondary sexual characteristics and testicular degeneration.¹³

Patients with Klinefelter syndrome rarely present for precocious puberty¹⁴. To date, only one patient with a Klinefelter syndrome variant (48, XXXY) and central precocious puberty (CPP) has been described.¹

We report here the first patient with 48,XXYY karyotype and precocious puberty.

PATIENT REPORT

Our patient was an 11.⁹/₁₂ year-old white male who was sent to us for psychomotor delay and sexual precocity. The child was born at term by caesarean section; his birth weight and length were 3800 g and 51 cm, respectively. After birth, he showed delayed psychomotor development. At about the age of 7 years, the parents noticed the appearance of pubic hair, increase in penile length and gynecomastia; the diagnosis of CPP was made in another hospital.

At our first examination, the patient presented facial dysmorphism (hypertelorism, micrognathia, large low-set ears), small hands and feet, small café-au-lait spots on thorax, gynecomastia, and advanced pubertal development (Fig. 1). He also had increased height and penile length, but small testes (Table 1). He did not have eunuchoid habitus (Table 1). Bone age was advanced and predicted adult height in the range of target height (Table 1). Family history was negative for abnormal sexual development. Neuropsychological examination showed mental retardation (verbal I.Q. 49; performance I.Q. 45; full score I.Q. 46) (WISC-R) with
learning disabilities and behavioral abnormalities (hyperactivity; deficits in attention, organization, and impulse control; shy and reserved; difficulty completing tasks; poor interpersonal relations; communication difficulties).

Endocrinological investigations demonstrated high levels of gonadotropins: basal LH 31.2 IU/l (normal value [n.v.] prepubertal <3.5 IU/l; pubertal 0.5-6.0); peak LH 130.6 IU/l (n.v. prepubertal <15.0; pubertal 7.0-25.0); basal FSH 91.7 IU/l (n.v. prepubertal <4.5; pubertal 1.0-7.0); peak FSH 142.4 IU/l (n.v. prepubertal <12.0; pubertal 2.0-11.0), with testosterone levels in lower normal range for adults (13.9 nmol/l [n.v. prepubertal <2.0; pubertal 10-35]). Basal and ACTH stimulated cortisol and 17-hydroxyprogesterone, ß-HCG, α-fetoprotein, prolactin and thyroid hormones were in the normal range (data not reported). The karyotype was 48,XXYY; chromosome analysis (n = 100 leukocytes) did not demonstrate mosaicism. The parents' karyotype was normal.

Chest X-ray and ultrasonography of the adrenal glands and the abdomen were unremarkable. Magnetic resonance imaging of the hypothalamus-pituitary region was negative for central nervous system abnormalities. Testicular biopsy showed a low number of atrophic tubules (Fig. 2). The tubul-
ar wall showed thickened basement membranes and tubules were populated by Sertoli cells. Germ cells were almost completely absent and no spermato- gonia or spermatozoa were observed. Abundant interstitial fibrosis and prominent crest of Leydig cells were present (Fig. 2).

The patient was re-evaluated at the age 13-5/12 years. Bone age was 17.0 years and his near final height (defined as height >99% of final height according to Bayley and Pinneau tables7) was adequate for target height and normal mean (Table 1). Endocrinological investigations confirmed the high serum basal levels of gonadotropins (LH 45.2 IU/l; FSH 130.2 IU/l) with testosterone serum values in the lower normal range for adults (14.5 nmol/l).

METHODS

Standing height was measured with a wall-mounted stadiometer and compared with Tanner tables8. Data are expressed as standard deviation score [SDS = (patient value – mean normal value)/SD of normal mean]. All values were expressed as standard deviation scores.

TABLE 1

<table>
<thead>
<tr>
<th>Auxological data at diagnosis and at near final height</th>
<th>At diagnosis</th>
<th>At final height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological age, yr</td>
<td>11-7/12</td>
<td>13-5/12</td>
</tr>
<tr>
<td>Bone age, yr</td>
<td>15-3/12</td>
<td>17</td>
</tr>
<tr>
<td>Bone age, SDS</td>
<td>+4.93</td>
<td>+4.31</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.5</td>
<td>176.0</td>
</tr>
<tr>
<td>Statural age, yr</td>
<td>16-6/12</td>
<td>adult</td>
</tr>
<tr>
<td>Height, SDS for CA°</td>
<td>+2.68</td>
<td>+2.36</td>
</tr>
<tr>
<td>Height, SDS for BA°°</td>
<td>-0.67</td>
<td>+0.25</td>
</tr>
<tr>
<td>Upper/lower segment ratio, SDS*</td>
<td>+0.09</td>
<td>-0.18</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.9</td>
<td>86.1</td>
</tr>
<tr>
<td>Weight excess for height, %</td>
<td>53.0</td>
<td>65.0</td>
</tr>
<tr>
<td>Pubertal stage</td>
<td>Ph4</td>
<td>Ph5</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>B2/3</td>
<td>B3</td>
</tr>
<tr>
<td>Testes dx/sx, SDS for Ph stage</td>
<td>-1.43 / -1.25</td>
<td>-2.8 / -2.5</td>
</tr>
<tr>
<td>Penis length, SDS for CA</td>
<td>+3.00</td>
<td>+1.42</td>
</tr>
<tr>
<td>Penis length, SDS for BA</td>
<td>-1.75</td>
<td>-1.19</td>
</tr>
<tr>
<td>Mid-parental height, cm</td>
<td>168.0</td>
<td></td>
</tr>
<tr>
<td>Range target height, cm</td>
<td>159.5 - 176.5</td>
<td></td>
</tr>
<tr>
<td>Predicted adult height, cm</td>
<td>171.6</td>
<td>176.2</td>
</tr>
<tr>
<td>Predicted adult height - mid-parental height, cm</td>
<td>+3.6</td>
<td>+8.2</td>
</tr>
</tbody>
</table>

*CA = Chronological age; °°BA = bone age; *according to statural age.
calculated taking into account both chronological age and bone age. Upper/lower body segment ratio was determined according to Arad and Laron. 

Pubertal development was studied according to Tanner & Whitehouse only for pubic hair development, because testicular size is not a valid index of pubertal development in patients with Klinefelter syndrome. Gynecomastia was graded according to the stages of breast development in females. Testicular size was measured by Prader orchidometer and expressed in SDS using the normative data of Zachmann et al. according to chronological age and bone age. Penile length was expressed as SDS according to Schonfeld’s and Beebe’s normative values.

Bone age was evaluated using the Greulich and Pyle method. Predicted adult height was calculated using the Bayley and Pinneau method. Mid-parental height was obtained by using the measured parental heights [(father’s height plus mother’s height plus 12.5) cm/2]. The range of target height was calculated by adding and subtracting 8.5 cm to the mid-parental height.

The GnRH test were performed in the following manner: GnRH (100 μg; Serono, Switzerland) was administered by intravenous injection after basal sampling for LH, FSH, testosterone, β-HCG, α-fetoprotein and thyroid hormones. Serum for LH and FSH determination was obtained at 15, 30, 60 and 90 minutes. ACTH test was performed by intravenous ACTH administration (0.25 mg; Synacthen, Ciba, France); basal and stimulated 17-hydroxyprogesterone levels were analyzed by the nomogram of New et al. All tests were performed during the morning (8.00-9.00 AM); blood samples were centrifuged at 4°C within 1 hour after withdrawal, aliquoted in 1.0 ml serum fractions, and stored at -20°C until assayed. Serum levels of LH, FSH, testosterone, cortisol, 17-hydroxyprogesterone, thyroxine, triiodothyronine, TSH, β-HCG, and α-fetoprotein were measured by commercially available kits. For all measurements, inter-assay variability was less than 9% and intra-assay variability less than 7%.

Informed consent was obtained from both the parents of the proband, and the ethical committee for human investigation of our departments approved the study.

DISCUSSION

Klinefelter syndrome is the most common cause of primary hypogonadism in males. However, this syndrome is rarely diagnosed in childhood because

Fig. 2: Gonadal biopsy specimen of the patient (karyotype 48,XXYY): atrophy of testicular tissue with irregular tubules populated by Sertoli cells; interstitial fibrosis and crests of Leydig cells are evident. Testicular tubules show thickened basement membranes and Sertoli cells. Spermatogenesis was absent (Hematoxylin-eosin x 250).
boys with 47,XXY karyotype show relatively few clinical abnormalities. The ~120 patients described with 48,XXYY karyotype differ from classical Klinefelter syndrome in the greater severity and prevalence of mental retardation and psychiatric or behavioral disorders. Additional features are tall stature, gynecomastia, unusual dermatoglyphic pattern, and body disproportion. As a consequence, there is an increased probability that they will come to the attention of physicians earlier than those with classical Klinefelter syndrome. Our patient did not show the peripheral vascular disease that is an additional main clinical finding of men with 48,XXYY karyotype. Similar observations have been made in other prepubertal or adolescent patients, suggesting that this feature appears at an older age and it is probably not important for diagnosis in childhood.

Our patient had precocious puberty in addition to mental retardation and dysmorphic features. Although the first diagnosis of CPP was not supported by objective data, no other clinical evidence explained the clear advanced pubertal development and bone age we found. The patient lacked body disproportion at our first observation as well as at final height. Since precocious pubertal onset increases the growth of the trunk more than that of the limbs, it may lead to normal body proportions in our boy, as previously reported in patients with classical Klinefelter syndrome and CPP. Eunuchoid proportions have been observed in a boy with 48,XXXX karyotype and CPP, suggesting that the precocious onset of puberty does not ameliorate body proportion in all patients.

To our knowledge, the present patient is the first one reported with a 48,XXYY karyotype and CPP. The association between 48,XXYY karyotype and CPP has been reported in one patient, while the association of classical Klinefelter syndrome and precocious puberty has been reported in 14 boys. In eight boys, precocious sexual development was due to peripheral endocrinologically active malignancies. In the other patients and in the present boy, CPP was diagnosed. A hamartoma of the third ventricle was found in one boy and a pineal tumor in another. In the other patients, no organic alteration of the central nervous system was identified and CPP was considered "idiopathic".

While idiopathic CPP predominates in girls, it is diagnosed in a minority of boys in whom CPP is more frequently the consequence of an organic brain lesion. Since the majority of boys with Klinefelter syndrome had idiopathic CPP, the extra X chromosome may predispose these patients to idiopathic precocious onset of puberty.

The goal of treatment in CPP is halting or reversing the deterioration of height potential. In our patient, predicted height was comparable to target height and so he was not treated. In girls with CPP, lower plasma estradiol levels characterize the so-called "slowly progressive variant" which does not require treatment because normal final height is reached. Testosterone levels in patients with Klinefelter syndrome are in the normal range during the first stages of pubertal development; later on, hormone levels do not increase, remaining in low-normal range until adulthood because of testicular failure. These low-normal testosterone values likely permit the reaching of adequate adult height in spite of the CPP. Final height in untreated patients with Klinefelter syndrome and CPP was in the normal range for Klinefelter syndrome, as in our patient.

Pathological studies in 48,XXYY patients have been rarely performed, so the natural history of histological testicular findings is largely unknown. Bloomgarden et al. reported tubular atrophy, absent spermatogenesis, and peritubular fibrosis associated with hyperplasia of interstitial cells in adult patients. Grumbach and Conte studied a boy with 48,XXXY and CPP histologically and suggested that the premature increase in gonadotropin levels accelerated hyalinization and fibrosis of the testicular tubules. Our patient had elevated gonadotropins, tubular and peritubular fibrosis, germinal aplasia and clumping of Leydig cells. Thus, our data agree with the hypothesis that the increase of gonadotropin levels at puberty plays a role in testicular tissue degeneration in patients with Klinefelter syndrome. However, Muller et al. demonstrated degenerative changes of testicular histology also in prepubertal patients, suggesting that abnormal testicular development is the rule in Klinefelter syndrome after infancy, independent of gonadotropin levels. Further studies are needed to clarify the histology and pathogenesis of testicular
degeneration in Klinefelter syndrome and its variants.

In conclusion, we report the first boy with 48,XXYY Klinefelter syndrome variant and CPP. Since the occurrence of CPP seems to be increased in Klinefelter syndrome, karyotype analysis is advisable in boys with mental retardation, gynecomastia, small testes and precocious onset of puberty.

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