

Central precocious puberty as a prelude to hypogonadism in a patient with Klinefelter syndrome

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ABSTRACT

Introduction: Incomplete pubertal development is a common phenomenon found in patients with Klinefelter syndrome (KFS). KFS combined with central precocious puberty (CPP) rarely occurs. We herein report a rare case of KFS with CPP and review several studies to determine the possible mechanism underlying this condition.

Case presentation: An 8-year, 5-month-old male patient was admitted to our hospital because of enlargement of the penis and small testes. Laboratory evaluation revealed high luteinizing hormone and follicle-stimulating hormone levels, a high testosterone level, and the 48,XXYY karyotype. He was treated with triptorelin. One year later, the patient's testosterone level decreased and pubertal arrest occurred.

Conclusion: The literature review in this study showed that the occurrence of hypogonadism combined with CPP is not unique to patients with KFS; it has also been reported in individuals with Turner syndrome, adrenal hypoplasia congenita, and other diseases. Such individuals share common features including partial hypogonadism and a normal hypothalamic-pituitary-gonadal axis. CPP is considered a prelude to hypogonadism, and treatment with a gonadotropin-releasing hormone agonist may prevent gonadal failure.

KEYWORDS

Central precocious puberty, 48,XXYY, Klinefelter syndrome, Hypogonadism, Turner syndrome

INTRODUCTION

Sexual precocity is the appearance of any sign of secondary sexual maturation before the age of 8 years in girls and 9 years in boys. If sexual precocity results from premature reactivation of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator/hypothalamic-pituitary-gonadal (HPG) axis, the condition is GnRH-dependent and termed central precocious puberty (CPP). Pulsatile release of luteinizing hormone (LH) exhibits a

pubertal pattern, and the rise in the concentration of LH after GnRH administration is indistinguishable from the normal pubertal pattern of the serum LH concentration.

Klinefelter syndrome (KFS) is a type of male primary hypogonadism characterized by an extra copy of the X chromosome. KFS is mainly found in individuals with testicular dysplasia, azoospermia, infertility, and similar abnormalities. It was first described by Klinefelter in 1942. KFS accounts for about 3.1% of cases of male

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infertility and is the most common form of male gonadal dysfunction. KFS is divided into two forms according to the chromosomal karyotype: the classic form (47,XXY [83.4%]) and mosaic form (48,XXXY, 48,XXYY, 49,XXXXY, etc.).¹ Among these forms, 48,XXYY KFS is the rarest chromosome karyotype, with an incidence of 1:18 000 to 1:40 000; to date, only around 120 cases have been reported worldwide.^{2,3}

Incomplete pubertal development commonly occurs in individuals with KFS, whereas KFS with CPP rarely occurs. Here we report a case of a patient with 48,XXYY KFS with CPP and review the literature on this rare condition to explore the possible mechanisms underlying the co-occurrence of KFS and CPP.

CASE REPORT

The patient in this case was an 8-year, 5-month-old boy who had been regarded as normal until his parents found that he had begun growing rapidly during the past 2 years and that his penis had been increasing in size to that of an adult penis and erecting frequently; additionally, his pubic hair began appearing within the previous 5 months. He was then admitted to our hospital. The patient had grown at a rate of 10 to 15 cm/year without experiencing any discomfort. No spermatorrhea, acne, or voice changes were noted. He had no family history of KFS, his mother had not experienced problems during pregnancy, and he had no significant medical history.

Physical examination upon admission revealed a height of 153.5 cm (> 97th percentile), distance between the fingertips of 156 cm, and weight of 38 kg. The patient's vital signs, hair distribution, gait, and most facial features were normal. However, slowed movement and clumsiness were noted. He had a slightly wide nose wing and thick lip. He also had problems stretching his elbows and exhibited poor distal interphalangeal joint motion of both hands. A single palmar crease, knock knees, and flat feet were noted. The patient's muscle volume and strength were good. The following findings were also noted: breasts, Tanner I; pubic hair, Tanner II; penis length, 8.5 cm; penis diameter, 2.5 cm; bilateral scrotum, normal in appearance; testicular volume, 3 to 4 mL; and testicular texture, normal.

The patient's bone age was about 13 years. His social life ability score was equal to that of a 3- to 4-year-old child. Laboratory parameters were as follows: plasma adrenocorticotrophic hormone and serum cortisol levels, normal; LH, 5.65 mIU/mL; serum follicle-stimulating hormone (FSH), 18.52 mIU/mL; testosterone, 2.63 ng/mL; estradiol, < 20 pg/mL; human chorionic gonadotropin, < 0.1 mIU/mL; anti-Müllerian hormone, 12 ng/mL (reference range, 1.43–11.4 ng/mL); and inhibin B, 33 pg/mL (reference range, 50–80 pg/mL). An LH-releasing hormone stimulation test was performed because of basal

LH/FSH imbalance, and the results were as follows: LH, 59.1 IU/L; FSH, 34.3 IU/L; and LH/FSH ratio, >0.6. The results of an adrenocorticotrophic hormone stimulation test were as follows: basal testosterone, 137 ng/dL; peak testosterone, 146 ng/dL; basal cortisol, 4.8 µg/dL; peak cortisol, 22 µg/dL; basal 17-hydroxyprogesterone, 2.37 ng/mL; and peak 17-hydroxyprogesterone, 2.81 ng/mL. His brain magnetic resonance imaging findings were normal, and all tumor markers were within the reference ranges. The results indicated hypergonadotropic hypogonadism combined with CPP, and his karyotype was 48,XXYY. To rule out other pathologies, whole-exome sequencing was performed and the results were negative. The patient's final diagnosis was KFS with CPP. He underwent GnRH agonist therapy to suppress the HPG axis. One year later, his height had increased by 8 cm, both of his testicles measured 4 mL, and his sex hormones were within prepubertal levels (LH, 0.8 IU/L; FSH, 2.3 IU/L; and testosterone, < 20 ng/mL).

DISCUSSION

We have herein reported a rare case of KFS combined with CPP. The patient had penis enlargement, a bilateral testicular volume of 3 to 4 mL, and very high LH and FSH levels. Further evaluation showed a strong LH and FSH response after the LH-releasing hormone test, which indicated premature reactivation of the hypothalamic GnRH pulse generator/HPG axis and verified his testicular impairment.

Focusing on KFS combined with CPP, we searched the literature using the keywords “Klinefelter,” “precocious puberty,” and “gonad dysplasia” in Medline, PubMed, Embase, and CNKI up to July 2017. Nine articles described precocious puberty^{4–12} and four articles^{5–8} described ectopic secretion of human chorionic gonadotropin by endocrine tumors (three cases of 47,XXY and one case of 48,XXYY). Another five articles described cases of non-mosaic KFS combined with central sexual precocity.

The main points addressed in previous discussions of patients with KFS combined with CPP are as follows^{4,10}: (1) the X chromosome dosage compensation effect, (2) involvement of the X chromosome in the abnormal expression of special genes, and (3) abnormal expression of the androgen receptor. However, these three mechanisms might not sufficiently explain the underlying cause of KFS combined with CPP for the reasons described below.

First, the dosage compensation effect of the X chromosome in normal people according to Lyon's theory balances the expression of the X and Y chromosomes. Most patients with KFS have impaired testicular function. Apparently, the additional X chromosome interferes with gonadal development because it disrupts the gene expression

balance. Most importantly, the occurrence of CPP cannot be explained by the presence of an extra X chromosome because no CPP gene has been found on the X and Y chromosomes. Some studies have suggested that an increased number of Y chromosomes could affect the HPG axis because the modulated genes involved in testicular development and spermatogenesis are mainly distributed on the Y chromosome, and multiple genes are involved in the modulation.^{13,14} However, this cannot explain why patients with KFS or those with classic forms of KFS with sexual precocity have higher numbers of X chromosomes. In our patient, the presence of two Y chromosomes may be partially explained by the compensation effect. Both 48,XXYY syndrome and XYY syndrome are characterized by variant gonadal dysgenesis instead of CPP. All of this evidence indicates that regardless of the sex chromosome doses, the balance exerts a true and significant effect on the integrity of gonadal function.¹⁵

Second, the genes on the X chromosome, including those in the Xq24 region, are responsible for development of the ovaries. They do not depend on the HPG axis in the early stage of embryonic development. It has been assumed that abnormal expression of a special gene on the X chromosome causes sexual precocity. However, no study has verified an association between an X-linked gene and the occurrence of sexual precocity.

Third, abnormal androgen receptor expression might be an indication of a hypersensitive or insensitive syndrome instead of CPP. KFS is diagnosed in the presence of peripheral precocious puberty or a disorder of sex development such as androgen insensitivity syndrome. Hence, the above three factors cannot reasonably explain the presence of CPP.

Therefore, we hypothesize that KFS with CPP occurs by partial impairment of the gonads, which activates the HPG axis and thus lead to CPP. We searched the literature (Medline, PubMed, Embase, and CNKI) using the keywords “central precocious puberty,” “hypogonadism,” “Turner syndrome,” and similar terms, and the results showed that gonadal dysplasia with CPP is not unique to KFS. Similar to KFS, other disorders also occur along with CPP, including Turner syndrome¹⁶⁻²⁰ adrenal hypoplasia congenita.^{21,22} All such disorders share the same features: a normal HPG axis, hypogonadism, and the presence of residual gonadal function. All of these diseases are related to early activation of the HPG axis, leading us to conclude that CPP is a prelude to hypogonadism.

Considering that gonadal cells may undergo early apoptosis resulting in eventual premature gonadal failure with high gonadotropin hypogonadism, our patient received a GnRH agonist not only to treat the CPP but also to protect against premature gonadal failure. After 1 year of follow-up, good suppression of the HPG axis was achieved.

CONFLICT OF INTEREST

All authors declare that no conflicts of interest exist regarding this work.

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