*Case Report*

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# Turner syndrome with rapidly progressive puberty: a case report and literature review

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**Abstract**

This report describes a clinically rare and atypical case of 46,X,idic(X)(q21.32)/45,X-type Turner syndrome with rapidly progressive puberty development. After 11 months of treatment with recombinant human growth hormone (rhGH), the child's height increased. After 18 months of treatment with rhGH, the child showed secondary sex characteristics. The child was followed up for 1 year after the appearance of the secondary sex characteristics, and regular menses were still present. This case indicates that modern molecular biology techniques should be used rationally to further investigate the existence of X-chromosome translocations and occult chimeras to prevent misdiagnosis.

**Keywords**

Turner syndrome, puberty development, recombinant human growth hormone, secondary sex characteristics, chromosomal abnormality, karyotype

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## Introduction

Turner syndrome (TS), also known as congenital ovarian hypoplasia syndrome, is the only monomeric syndrome that humans can survive. TS is caused by the complete or partial deletion of an X chromosome in all or a portion of the somatic cells. First reported by Turner in 1938,[1] TS is a common human chromosomal abnormality. In 2006, a study from Denmark showed that the incidence rate in live-born females was about 1/2500 and that the incidence in live births was about 1/40,002.[2] The karyotypes of TS are 45,X and 45,X/46,XX.[3] The relationship

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between the genotype and phenotype of TS remains unclear. We herein describe a rare case of TS with the 46,X,idic(X)(q21.32)/45, X karyotype and rapidly progressive puberty development. We also review the natural history of TS.

## Case report

This study was approved by the Ethics Committee of the Children's Hospital of Nanjing Medical University. Written informed consent was provided by the patient's parents.

A 9.67-year-old girl was admitted to the Children's Hospital of Nanjing Medical University hospital on 22 October 2016 because of a >9-year history of slow growth. The child was born as the second fetus of the mother's first birth; the first fetus had been spontaneously aborted. The child was delivered naturally at full term with a birth weight of 2.5 kg and an unknown body length. She had no history of intrauterine distress and no asphyxia after birth. The height of her father and mother was 168 and 152 cm, respectively, and her mother had first developed menarche at 13 years of age. The patient's paternal and maternal lines contained no males with a height of <160 cm and no females with a height of <150 cm.

On physical examination, the patient's height was 119.1 cm (below the third percentile of the growth curve of normal healthy girls of the same age), and her weight was 25.5 kg. She had stage B1 bilateral breasts with a wide breast distance, no pigmentation on the breast surface, a shield-like chest, and webbing of the neck. She also had mild cubitus valgus, slightly obvious warped hips, and a girlish vulva without pubic hair growth. No abnormalities were found in the cardiopulmonary examination, urine and fecal examinations, liver and kidney function, and electrolyte levels. Blood testing showed a fasting blood glucose level of 4.44 mmol/L, glycated hemoglobin level of 5.2%, insulin level of 8.24 mIU/L, and C peptide level of 0.542 ng/mL. The thyroid function test results were within normal limits. The levels of sex hormones were as follows: estradiol, <18.35 pg/mL; progesterone, 0.462 ng/mL; testosterone, <0.087 ng/mL; follicle-stimulating hormone (FSH), 20.36 mIU/mL; luteinizing hormone, 1.02 mIU/L; human chorionic gonadotropin, <0.500 MoM; carcinoembryonic antigen, 1.58 ng/mL; alpha-fetoprotein, 1.01 ng/mL; cortisol, 182.2 nmol/L; adrenocorticotropic hormone, 9.18 pg/mL; and insulin-like growth factor 1, 266 ng/mL. The "two and a half pairs" test was performed for hepatitis B virus infection, and the result showed that hepatitis B surface antibody was weakly positive without other abnormalities. Arginine–clonidine growth hormone (GH) stimulation testing revealed that the GH peak was 11.259 ng/mL. X-ray examination showed that the patient's bone age was equivalent to 9 years, and no abnormalities were observed in the anteroposterior or lateral film. Nodal tachycardia was found on an electrocardiogram. Pituitary magnetic resonance imaging demonstrated no abnormalities, and breast ultrasonography detected no breast tissue. Gynecological ultrasonography revealed that the size of the uterine body was $23 \times 10 \times 9$ mm and that the size of the right ovary was $15 \times 11 \times 10$ mm with one >4-mm follicle; the left ovary was not clearly seen.

The child was diagnosed with TS due to a missing X chromosome (45,X karyotype). She was then treated with recombinant human GH (rhGH). After 11 months of rhGH treatment, the child's height had increased by 8.2 cm (annual growth rate of 8.9 cm/year). After 18 months of follow-up, the child's height had increased by 12.9 cm (annual growth rate of 8.6 cm/year). No breast development had occurred at the age of 10 years 11 months. At the age of 11 years 2 months, stage B2 to 3 bilateral

breast growth was found and menarche was present. Breast ultrasonography showed breast echoes of $51 \times 14\,mm^2$ and $45 \times 15\,mm^2$ in the right and left breast regions, respectively, indicating bilateral breast enlargement. Gynecological ultrasonography revealed an increase in the size of the uterine body ($34 \times 16 \times 17\,mm$) and morphological development (visible endometrium) with unclear bilateral ovaries. The levels of estradiol, progesterone, testosterone, FSH, and luteinizing hormone were 134.1 pg/mL, 0.334 ng/mL, <0.087 ng/mL, 8.03 mIU/mL, and 2.03 mIU/L, respectively. The patient's bone age was equivalent to 11 to 12 years. Chromosome microarray analysis indicated 46,X,idic(X)(q21.32)/45,X, where 45,X had a chimeric ratio of approximately 90%. No abnormalities were found in whole-exome sequencing. Because the parents refused to use a gonadotropin-releasing hormone agonist (GnRHa), the child continued treatment with rhGH. At the time of this writing, the child was 12 years 6 months old with a height of 141 cm, had B3 to 4 bilateral breast growth, had a bone age of 13 to 13.5 years, and had regular menses.

## Discussion

45,X is the most common karyotype of patients with TS and accounts for about 50% of all cases. This karyotype is mainly caused by nondisjunction during the first meiosis of the sex chromosomes of the father's or mother's germ cells. Another 20% to 30% of cases are chimeric (45,X/46,XX), and the remaining cases involve X-chromosome structural abnormalities; some patients also have a Y chromosome at the same time.[3] The chromosome karyotype is complex and the phenotypes are diverse in patients with TS. Typical manifestations include facial paralysis, webbing of the neck, a shield-like chest, cubitus valgus, short stature, no breast development after puberty, no menstrual menarche, and other types of gonadal dysplasia. With respect to the clinical manifestations of the 45,X chromosome chimeric karyotype, the severity of the phenotype and gonadal differentiation depend on the ratio of 45,X cells to normal cells among the somatic and germ cells during differentiation. A higher ratio of normal cells results in a more normal human phenotype.

Patients with TS may develop spontaneous puberty, menarche, and even pregnancy, and most of these patients are chimeras.[4–6] Because of the lack of an X chromosome, during the embryonic period of 45,X patients, most of the ovarian tissue is fibrotic, a large number of oocytes and follicular cells have degenerated, almost no germ cells or follicles are formed, and only a small amount or no sex hormone is produced, leading to ovarian insufficiency in adolescence. Therefore, the spontaneous development of this type of monomeric patient is relatively rare. In a retrospective study in Italy,[7] the proportion of spontaneous puberty in monosomy 45,X was 22.4%, while the probability of spontaneous menarche was only 9.2%. Lippe et al.[8] found that only 8.8% of monosomy 45,X patients had ovarian function, which is a far lower proportion than that of patients with other karyotypes. The Lyon hypothesis is that one X chromosome in 46,XX is inactivated and that 45,X is missing this inactive X chromosome, which is also why monosomy 45,X individuals can survive. However, not all genes on the inactivated X chromosome are inactivated, and these un-inactivated genes may still play a role in the regulation of gonadal development. The spontaneous development of patients with the 45,X karyotype may also be related to the presence of chimeric karyotypes in ovarian tissue.[9,10] With the development of gene technology, fluorescence *in situ* hybridization analysis of buccal cells using a specific probe technique for typical patients with the 45,X karyotype revealed that

about 30.2% of patients had a second or third cell line.[11]

No chimera was found in our patient by routine chromosome examination. Because the number of cells used in the conventional peripheral blood lymphocyte karyotype analysis is usually 30, the diagnosis is difficult when the proportion of the chimera is <10%. Therefore, we used chromosome microarray analysis and found that the child's karyotype was 46,X,idic(X)(q21.32)/45,X (the chimera ratio of 45,X was about 90%). A deletion of approximately 92.22 Mb for Xp22.33q21.32 and a deletion of approximately 63.05 Mb for Xq21.32q28 were present. Genes related to ovarian function are believed to be present in the long arm (q) and short arm (p) of the X chromosome. The ovarian phenotype is mainly related to the two regions (Xq13-Xq21 and Xq23-Xq27) in the long arm of the X chromosome, and rupture or gene loss in these regions leads impaired ovarian function.[12] For Xq proximal loss (such as Xq13), clinical manifestations are usually more serious, including lack of breast development, primary amenorrhea, and gonadal failure. The Xp deletion is caused by breakage of the short arm and long arm in the centromere portion; the short arm is accompanied by the centromere portion, and the long arm is lost because of the absence of the centromere portion during replication. Deletion of Xp11 results in ovarian failure in approximately 50% of patients.[13] Loss of distal Xp can lead to short stature and physical characteristics of TS, but the gonadal function is usually preserved; menstruation can often occur with the loss of Xp21.1-p22.1 or Xp22.2, but many patients are still infertile or have secondary amenorrhea.[14] Patients with serotypes of idic(X) are very rare. The incidence rate is about 1/13,000 live births, and most of them appear in 45,X/46,X,idic (Xq) chimeras.[15] The breakpoints on the top are commonly found in, e.g., Xq13, Xq21, Xq22, Xq27, and Xq28. The clinical characteristics and sexual development of patients differ based on the degree of chimerism and the location of the breakpoint. The karyotype of our patient was 45,X and 46,X,idic(X)(q21.32), 90% of which was 45,X. The child had typical TS characteristics when starting treatment. During rhGH treatment, breast development and menarche emerged, and the rate of development increased. Considering the rapid progression of puberty, this type of TS has not been reported. In this case, the X chromosome formed by the arm-derived chromosome resulted in deletion of the long-arm fragment, which involved the ovarian function area of the long arm of the X chromosome, and 90% of the child's karyotype was 45,X. The cause of the second sexual feature remains unknown. In recent years, cases of central precocious puberty in patients with TS have also been reported.[16–18] The specific mechanism remains unknown, but it may involve an abnormality of the hypothalamic feedback system as well as the compensatory gonadotropin and increased FSH in patients with remaining ovarian function.[19]

The United States Food and Drug Administration approved the use of rhGH in 2003 to improve adult height of patients with TS. rhGH can effectively increase the adult height of patients with TS, but the degree of the height increase depends on the height at the start of treatment, genetic height, age at treatment, course of treatment, and dosage. However, no relevant guidelines are available for the use of GnRHa to treat precocious puberty combined with rapidly developing puberty in patients with TS. The existing literature describes the use of GnRHa combined with rhGH[14,18,20] or GnRHa alone.[21,22] In the present case, the patient's bone age progressed during follow-up, but after repeated communication with the parents, the parents refused to use GnRHa and the patient therefore continued rhGH treatment for ovarian function. Although

menarche was still present at the time of this writing, the patient's ovarian function will not necessarily persist; therefore, we will continue to follow up the patient. In addition, patients with TS have only a 2% to 5% chance of spontaneous pregnancy, but the risk of spontaneous abortion, stillbirth, congenital anomalies, and aneuploidy is significantly increased[4,23]; therefore, prenatal counseling and prenatal diagnosis should be recommended.

This is the first report of a patient with 46, X,idic(X)(q21.32)/45,X-type TS who showed rapidly progressive puberty, which is clinically rare and atypical. Modern molecular biology technologies should be rationally applied to further investigate whether patients carry X-chromosome translocations and occult chimeras to prevent misdiagnosis.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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