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Primary Amenorrhea as the Initial Presentation of Triple X Syndrome: Three Case Reports

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Abstract
Trisomy X is characterized by a wide spectrum of clinical presentations and may remain underdiagnosed because of its often subtle expression. Clinical manifestations are variable and may include normal or increased stature, learning difficulties, menstrual disturbances, and, in certain cases, premature ovarian insufficiency. Mosaic forms involving 45,X or 46,XX may be associated with more severe phenotypes such as growth retardation and hypergonadotropic hypogonadism, and the diagnosis is established by karyotype analysis. We report three observations illustrating the clinical variability of triple X syndrome. The first case concerns a 17-year-old girl with a mild phenotype who presented with primary amenorrhea despite complete pubertal development; karyotyping demonstrated homogeneous trisomy X (47,XXX), and spontaneous menstruation subsequently occurred. The second case involves a 17-year-old patient with growth retardation, delayed puberty, and dysmorphic features; cytogenetic analysis revealed a complex mosaicism 45,X / 46,XX / 47,XXX associated with hypergonadotropic hypogonadism. The third case is a 21-year-old woman, tall and in good general condition, who presented with primary amenorrhea related to primary ovarian failure; investigations identified a 47,XXX karyotype associated with uterine hypoplasia. These observations highlight the marked clinical heterogeneity of trisomy X, ranging from a nearly normal phenotype to presentations resembling Turner syndrome, with diverse modes of presentation including primary amenorrhea with normal pubertal development, severe pubertal delay, and primary ovarian failure. The variability of clinical presentations supports the use of karyotype analysis in the evaluation of pubertal or reproductive disorders, including primary amenorrhea, growth delay, and hypergonadotropic hypogonadism.

Keywords: Triple X Syndrome , Primary Ovarian Failure , Primary Amenorrhea , Karyotype Analysis , Fertility Preservation , Growth Abnormalities

Introduction

The 47,XXX genotype, or X trisomy, is a sex chromosome abnormality characterized by the presence of an extra X chromosome, responsible for a highly variable phenotype [1] . It is the most common female chromosomal abnormality, estimated at 1 case per 1,000 female births [2]. Despite this high prevalence, barely 10% of cases are diagnosed [2] .

The non-mosaic form is the most common, but mosaicism is found in more than 10% of cases, sometimes in association with Turner syndrome cell lines [2] .

Although the majority of patients with trisomy X do not have major medical complications, certain abnormalities may be associated with it, including genitourinary malformations ranging from unilateral renal dysplasia to ovarian abnormalities

The onset of puberty and sexual development are generally normal in X trisomy. However, some patients report menstrual difficulties, oligomenorrhea, and delayed menarche or premature ovarian failure (POF)

We report three cases illustrating the diversity of clinical manifestations associated with the 47,XXX genotype and gonosomic mosaicism, revealed in various endocrine contexts: primary amenorrhea with normal puberty, severe pubertal delay, and primary ovarian failure. This series highlights the importance of considering the 47,XXX spectrum in the evaluation of pubertal and reproductive development disorders.

Case Presentation

Case 1

This is a 17-year-old patient born to non-consanguineous parents who was admitted to our department for evaluation of primary amenorrhea. Clinical examination showed that she was in good general condition, with normal blood pressure (100/63 mmHg). She presented with right thoracic scoliosis associated with dorsal hyperkyphosis and a right gibbosity measuring 14 cm in height, without other deformities. Her weight was 30 kg (−3 SD), height 1.50 m (−2 SD), and BMI 13.3 kg/m² (underweight), with Tanner stage V secondary sexual characteristics and no associated dysmorphic features (Figure 1 - Case 1).

Hormonal evaluation showed normal gonadal function, with estradiol at 131 pg/mL, FSH at 7.07 mIU/mL, and LH at 3.85 mIU/mL. Cytogenetic analysis demonstrated a homogeneous 47,XXX karyotype (Figure 2 - Case 1). Pelvic ultrasound revealed a normal-sized anteverted uterus with regular contours and a homogeneous endometrium. Both ovaries were visualized and appeared normal. Screening for associated abnormalities was unremarkable, including thyroid function assessment, bone metabolism evaluation, autoimmune screening, and morphological examination of the urinary tract. The clinical course was marked by the spontaneous onset of menstruation.

Case 2

The second patient, aged 18 years and three months, born to non-consanguineous parents, was admitted for evaluation and management of growth retardation and primary amenorrhea. Clinical examination revealed a height of 141 cm (−4 SD) and a weight of 31 kg (−3.2SD). She presented with dysmorphic features including a triangular face, pectus excavatum . External genitalia were normal in appearance, with no palpable inguinal mass. Tanner staging showed breast stage I, pubic hair stage IV, and sparse axillary hair.

Hormonal assessment revealed hypergonadotropic hypogonadism. Bone age was estimated at 13-14 years according to the Greulich and Pyle method. Cytogenetic analysis confirmed mosaic Turner syndrome with three cell lines: 45,X / 46,XX / 47,XXX and negative SRY (Figure 3 - Case 2)

Case 3

The third patient, aged 23 years and born to first-degree consanguineous parents, was admitted for evaluation of primary amenorrhea. Clinical examination showed good general condition, normal blood pressure, weight 59 kg (mean), height 1.72 m (+1.5 SD), Tanner stage V secondary sexual characteristics, and no associated dysmorphic features.

Hormonal evaluation revealed hypergonadotropic hypogonadism. Cytogenetic analysis demonstrated a 47,XXX karyotype. Pelvic ultrasound and magnetic resonance imaging showed the presence of a hypoplastic uterus. Screening for associated congenital malformations and autoimmune diseases was normal. Evaluation of complications related to hypogonadism was unremarkable. The patient was started on estrogen-progestogen hormone replacement therapy, with withdrawal bleeding occurring after three months of treatment. No clinical photographs or cytogenetic images were available for Case 3.

Figure 1: image of our patient with Trisomy X (case 1)

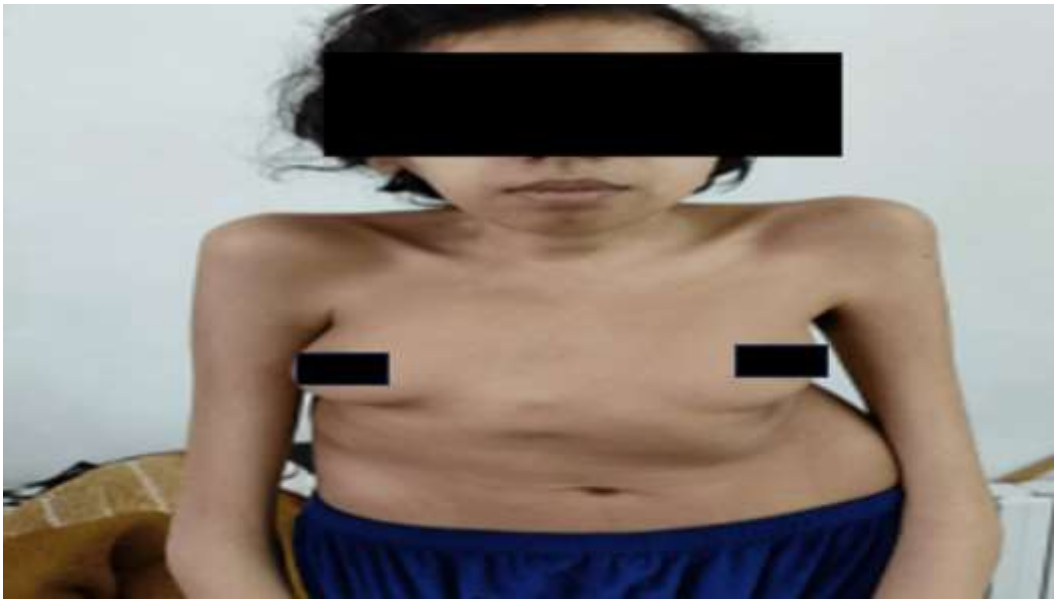


Figure 2: Karyotype of our patient showing Trisomy X (case 1)

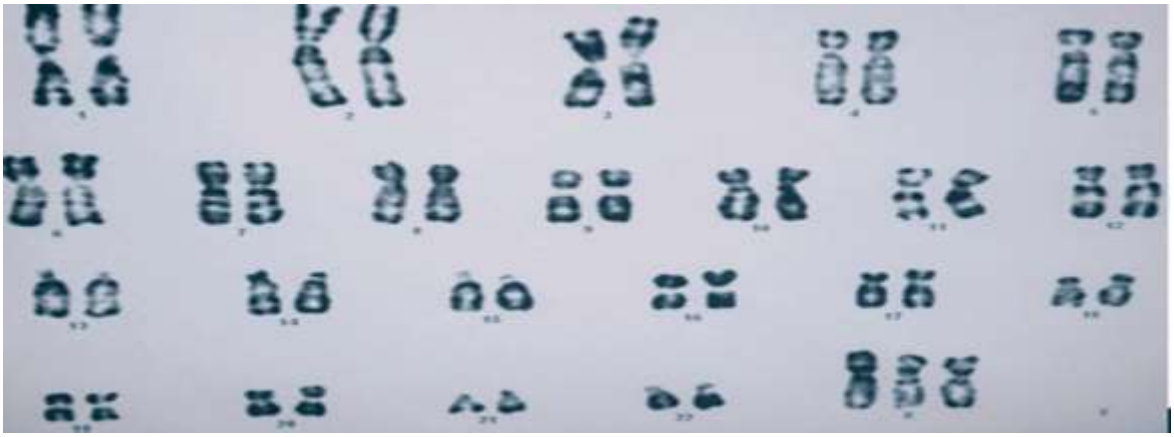
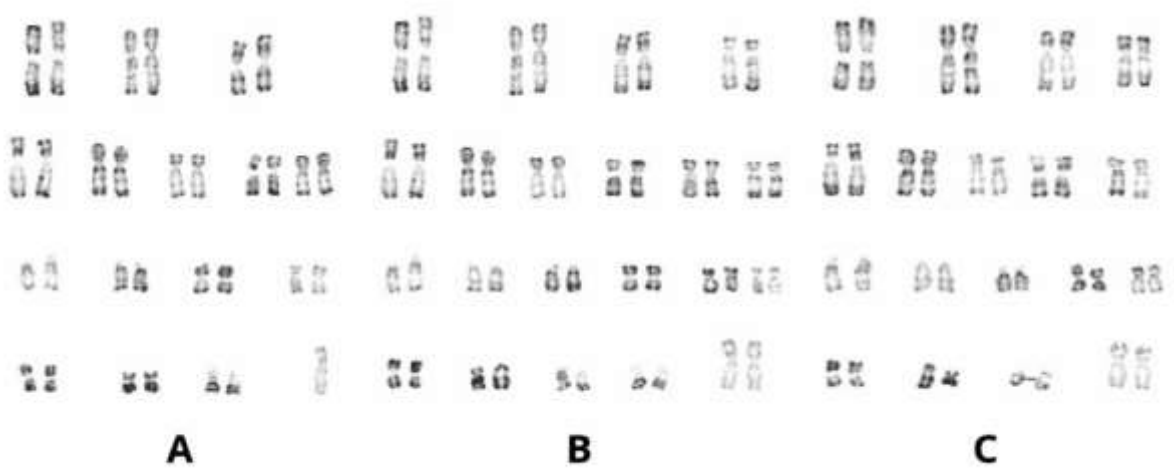


Figure 3: Image of our patient's karyotype showing the three cell lines (case 2)



Discussion

Trisomy X (47,XXX) is a sex chromosome aneuploidy characterized by the presence of an extra X chromosome in females, compared to the 46,XX karyotype of women without chromosomal abnormalities. It was first described in 1959 in a 35-year-old woman with normal intellectual abilities and secondary amenorrhea that began at age 19 [3] . Since this initial description, only a few hundred cases have been documented, revealing a wide variability in developmental, psychological, and medical manifestations.

Marked facial dysmorphism and characteristic physical features are not usually associated with 47,XXX syndrome. However, some minor physical signs may be observed, such as epicanthal folds, hypertelorism, slanted palpebral fissures, clinodactyly, overlapping fingers, flat feet, and pectus excavatum. Hypotonia and joint hyperlaxity may also be present. [2,4]

At birth, height and weight are generally within the normal range for gestational age. Growth tends to accelerate during early childhood and adolescence, with the majority of 47,XXX girls exceeding the 75th percentile for height [4] . Some cases are reported in association with tall stature, which justifies karyotyping in tall women [5] . Furthermore, cases of short stature have also been described, independent of 45,X mosaicism , and a prospective study identified a subgroup of 47,XXX girls whose height is below the 50th percentile [6] .

Although trisomy X is not generally associated with major medical problems, some complications can occur. Genitourinary anomalies are the most common, ranging from unilateral renal dysplasia to ovarian malformations [7] . Congenital heart defects have also been reported, including atrial and ventricular septal defects, pulmonary stenosis, and coarctation of the aorta [8,9] . Seizures are observed in approximately 15% of patients in the largest cohorts, including partial, generalized, or absence seizures, which are usually well controlled with standard antiepileptic medication [10,11] . Psychological disorders—major depression, anxiety, suicidal ideation, and low self-esteem—require specific clinical management [12,13] . Ultimately, these complications underscore the importance of multidisciplinary follow-up tailored to the individual needs of patients, including regular medical, psychological, and neurological assessments.

Our observations illustrate this phenotypic heterogeneity: the first patient (homogeneous 47,XXX) presented with marked growth retardation and severe thoracic scoliosis, manifestations rarely reported in this syndrome and whose association is not clearly established in the literature. Despite the presence of normal secondary sexual characteristics, primary amenorrhea was the reason for consultation, making this

an atypical case. The second patient, carrying a complex mosaicism 45,X/46,XX/47,XXX, presented with growth retardation, homogeneous pubertal delay, and dysmorphism suggestive of Turner syndrome, which corresponds to the phenotypes described in mosaicisms involving a monosomic lineage. The third patient (47,XXX) had normal height but marked hypergonadotropic hypogonadism, revealing ovarian insufficiency related to trisomy X.

In patients with trisomy X, puberty and sexual development are generally normal. However, cases of ovarian or uterine dysgenesis, as well as diminished ovarian reserve with accelerated loss of ovarian function, have been reported [3] . Since the first case described by Jacobs in 1959 in a woman with secondary amenorrhea, several observations have confirmed the existence of premature ovarian insufficiency (POI), although its prevalence remains uncertain. A genetic study has identified trisomy X in 3% of POI cases, often associated with other autoimmune diseases, particularly thyroid disorders [14] .Few studies have investigated ovarian function in young women with Texas Street syndrome (TXS). In 2016, Stagi et al. published a cross-sectional study evaluating the hypothalamic-pituitary-gonadal axis in 15 girls aged 7 to 12 years with TXS, compared to women of the same age and pubertal stage without TXS who underwent precocious puberty assessment [15] . Their results showed higher LH and FSH levels, lower estradiol and inhibin B concentrations, and reduced ovarian volume in patients with TXS. The case-control study by Davis et al. is the first to report AMH concentrations in girls with TXS. She concluded that these girls had significantly lower AMH levels than controls, reflecting a decrease in ovarian reserve [16] . Prior to the studies by Stagi et al. and Davis et al., most observational studies reported normal puberty and fertility in girls with TXS, including numerous pregnancies and live births [2] . However, these studies were small, and the assessments may not have been sensitive enough to detect more subtle differences.

Although fertility is normal in many cases, with pregnancies reported [2] , these data indicate that a subgroup of patients with Texas T syndrome (TXS) is at risk of ovarian insufficiency. Several mechanisms have been suggested: congenital anomalies of ovarian development, localized autoimmunity [17,18] , genetic abnormalities involving the POF1B, STS, XNPEP2, FMR-1, and USP9X genes [19,20] , or an imbalance in the expression of pro- and anti-apoptotic genes such as AIFM1 and BCORL1 [19] . Tissue mosaicism also remains a possibility. Clearly, further research is needed to understand the ovarian pathophysiology in women with TXS.

The three patients presented illustrate different manifestations of ovarian involvement: normal ovarian function with spontaneous cycles (case 1), and severe hypergonadotropic hypogonadism (cases 2 and 3), highlighting the need for individualized endocrinological monitoring. In this context, regular monitoring of ovarian function, including AMH and FSH/LH level measurements as well as ovarian volume ultrasound, is recommended. Fertility counseling should be offered early to inform patients about the risk of pelvic inflammatory disease (PID) and fertility preservation options. Screening for associated autoimmune diseases, particularly thyroid disorders, is also indicated. Finally, given the specific characteristics observed in our cases (growth retardation, scoliosis, dysmorphism, hypogonadism), a multidisciplinary approach involving endocrinology, gynecology, psychology, orthopedics and nutrition appears essential to optimize the quality of life of these patients.

Conclusions

The observations confirm the broad phenotypic variability of 47,XXX syndrome, from normal puberty with transient amenorrhea to hypergonadotropic hypogonadism and premature ovarian failure. These

findings highlight the need for multidisciplinary follow-up, including endocrinology, gynecology, psychology, and orthopedics. Early screening for ovarian abnormalities and consideration of fertility preservation are recommended. Karyotyping should be performed in all cases of delayed puberty, primary amenorrhea, or growth disorders, even without obvious dysmorphic features, to optimize management and prognosis

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