

Turner Syndrome with an Unbalanced Pericentric Inversion of the X Chromosome and Spontaneous Menarche: A Case Report

Gabriela Mintegui, MD*

Associate Professor of Endocrinology and Metabolism Clinic, School of Medicine, Hospital of Clinics, University of the Republic, Montevideo, Uruguay

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***Corresponding author:** Gabriela Mintegui, Associate Professor of Endocrinology and Metabolism Clinic, School of Medicine, Hospital of Clinics, University of the Republic, Montevideo, Uruguay

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ABSTRACT

Turner syndrome results from the complete or partial absence of the second sex chromosome and is characterized by broad genotypic and phenotypic heterogeneity. Short stature and ovarian dysfunction are common, although some patients retain ovarian activity and experience spontaneous menarche.

We report a girl evaluated from the age of 9 years 9 months for short stature and reduced growth velocity, without typical stigmata of Turner syndrome or initial pubertal development. Karyotyping showed a structural abnormality of one X chromosome consistent with a pericentric inversion. Fluorescence in situ hybridization confirmed an unbalanced pericentric inversion with breakpoints at Xp21 and Xq21, absence of the Xp21 signal, and partial monosomy of the X chromosome. The same pattern was observed in all 200 peripheral blood lymphocyte metaphases examined, with no evidence of mosaicism in this tissue.

Growth hormone therapy was started at 11 years 6 months, with a favorable auxological response. At age 12 years, she received estradiol valerate for 2-3 months, after which treatment was discontinued. Pubertal development and uterine growth continued without estrogen therapy, and spontaneous menarche occurred at age 14 years. She subsequently had irregular spontaneous menstrual cycles until age 18 years, followed by oligomenorrhea. Later testing showed an FSH level of 22 mIU/mL, LH of 14 mIU/mL, estradiol of 53 pg/mL, and anti-Müllerian hormone of 0.3 ng/mL, consistent with residual ovarian activity and diminished ovarian reserve.

Residual ovarian function and spontaneous menarche may occur in patients with nonmosaic structural rearrangements of the X chromosome. Integrating cytogenetic findings with pubertal, menstrual, and hormonal follow-up may improve assessment of ovarian prognosis and facilitate timely reproductive counseling.

Keywords: Turner syndrome; X chromosome; Pericentric inversion; Spontaneous menarche; Ovarian function

Introduction

Turner syndrome (TS) affects phenotypic females with one intact X chromosome and complete or partial absence of the second sex chromosome, together with one or more characteristic clinical features¹. In addition to 45 X monosomy, the cytogenetic spectrum includes mosaicism and structural abnormalities of the X chromosome¹.

Short stature and ovarian insufficiency are among its most common manifestations. However, the relationship between karyotype and phenotype is not absolute and is particularly complex in structural rearrangements of the X chromosome. Current guidelines therefore recommend longitudinal assessment of gonadal function¹.

Although accelerated depletion of ovarian follicles results in a high prevalence of ovarian insufficiency, spontaneous ovarian function may persist. A systematic review reported spontaneous thelarche in 32% and spontaneous menarche in 20.8% of patients; among those with X monosomy, the frequency of spontaneous menarche was 9.1%².

In nonmosaic structural rearrangements of the X chromosome, gonadal function varies according to the region involved. A systematic review of 487 patients found ovarian dysfunction in 78.8% overall, in 33.3% of patients with Xp21/Xp22 deletions, and in 94.6% of those with long-arm deletions³. These differences may inform prognosis but cannot predict the ovarian phenotype of an individual patient.

Table 1: Auxological, pubertal, hormonal, and ultrasonographic course.

Age	Height (cm)	GV (cm/year)	Pubertal development	FSH (mIU/mL)	LH (mIU/mL)	Estradiol (pg/mL)	Relevant findings
9y 9 mo	—	Reduced	Prepubertal	—	—	—	Referral for short stature
10 y 11 mo	129.5	6.0	Prepubertal	—	—	—	Uterus 33 × 10 × 6 mm
11 y 1 mo	130.0	6.0	Prepubertal	—	—	—	Uterus 29 × 5 × 6 mm
11 y 6 mo	132.0	—	Prepubertal	—	—	—	GH initiated
11 y 9 mo	134.0	—	No clinical pubertal development	2.0	0.04	44	No estrogen treatment
12 y 1 mo	138.0	12.2	Onset of breast development	—	—	—	Estradiol valerate for 2–3 months
12 y 5 mo	140.0	9.2	Progressive breast development	—	—	—	Estradiol discontinued
12 y 8 mo	144.0	10.1	Tanner B II–III / PH II	—	—	—	Bone age consistent with chronological age
13 y	146.5	—	Puberty progressing	5.6	2.0	58	Uterus 68 mm; endometrium 4 mm
13 y 4 mo	147.8	6.0	Tanner B IV / PH IV	—	—	—	No estrogen therapy
14 y	—	—	—	—	—	—	Spontaneous menarche
Later follow-up	—	—	—	22	14	53	AMH 0.3 ng/mL

Abbreviations: GV, growth velocity; GH, growth hormone; B, Tanner breast stage; PH, Tanner pubic hair stage; AMH, anti-Müllerian hormone.

Menarche occurred spontaneously at age 14 years, more than one year after estradiol had been discontinued. The patient had irregular spontaneous menstrual cycles until age 18 years, followed by oligomenorrhea. Later testing showed an FSH level of 22 mIU/mL, LH of 14 mIU/mL, estradiol of 53 pg/mL, and anti-Müllerian hormone of 0.3 ng/mL, findings consistent with residual ovarian activity and diminished ovarian reserve. Her final adult height was 162 cm.

Subtle phenotypic features, including cubitus valgus and a low posterior hairline, were documented during follow-up (Figure 2).

We describe a patient with TS caused by an unbalanced pericentric inversion of the X chromosome, with breakpoints at Xp21 and Xq21 and no mosaicism detected in 200 peripheral blood metaphases, who retained ovarian activity and experienced spontaneous menarche.

Case Presentation

A girl was referred at 9 years 9 months because of short stature and reduced growth velocity, with a preserved weight-to-height ratio. She had no obvious phenotypic stigmata of TS and no pubertal development. She had been born at term, weighing 3600 g and measuring 48 cm in length. Her midparental target height was 153.3 cm.

Evaluation of the somatotrophic axis showed a normal GH response to clonidine stimulation, with a peak of 12.2 ng/mL; IGF-1 and IGFBP-3 were within the age-specific reference ranges. Conventional karyotyping identified a structural abnormality of one X chromosome consistent with a pericentric inversion, which was subsequently characterized by fluorescence in situ hybridization (FISH).

During follow-up, short stature and the initial absence of pubertal development persisted, with bone age consistent with chronological age. Growth hormone was started at 11 years 6 months at a dose of 0.15 IU/kg/day. Auxological, pubertal, hormonal, and ultrasonographic findings are summarized in (Table 1). Height and growth-velocity curves are shown in (Figure 1).

Molecular cytogenetic characterization

FISH was performed using probes targeting Xp21, the X-chromosome centromere (DXZ1), and Xq21. The rearranged X chromosome lacked the Xp21 signal, retained the centromeric DXZ1 signal, and showed Xq21 in an altered topologic position relative to the centromere. The same pattern was observed in all 200 peripheral blood lymphocyte metaphases examined, with no evidence of mosaicism in this tissue. The molecular cytogenetic formula was 46,X,inv(X)(p21q21).ish inv(X)(p21q21)(DXZ1+,Xp21-,Xq21+).

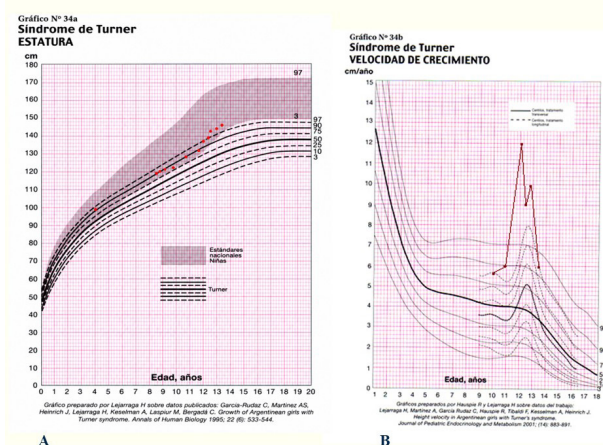


Figure 1: Auxological course during follow-up. A) Height curve relative to standards for girls with Turner syndrome. B) Growth velocity over time, showing acceleration after growth hormone treatment was initiated.



Figure 2: Phenotypic features of the patient. A) Upper-limb position consistent with cubitus valgus. B) Low posterior hairline.

The findings were consistent with an unbalanced pericentric inversion of the X chromosome associated with loss of the region recognized by the Xp21 probe and partial monosomy of the X chromosome.

Discussion

The patient had an unbalanced pericentric inversion of the X chromosome, with breakpoints at Xp21 and Xq21 and loss of the region recognized by the Xp21 probe. Despite the absence of detectable mosaicism in peripheral blood, she retained sufficient ovarian activity to complete pubertal development and experience spontaneous menarche at age 14 years. The initially subtle phenotype and presentation with short stature illustrate the phenotypic variability of TS and support cytogenetic testing in unexplained growth failure¹.

All 200 metaphases examined showed the same rearrangement. This finding excludes mosaicism detectable in peripheral blood lymphocytes by the method used, but it does not exclude very-low-level mosaicism or mosaicism confined to other tissues. Reproductive potential therefore cannot be inferred from the peripheral blood karyotype alone¹.

The review by Tanoshima et al. showed that ovarian dysfunction in nonmosaic structural X-chromosome rearrangements depends partly on the affected region and was less frequent with Xp21/Xp22 deletions than with Xq deletions⁽³⁾. These findings cannot be directly extrapolated to our patient, whose rearrangement is an unbalanced pericentric inversion rather than an isolated Xp21 deletion. Nevertheless, they confirm that a diagnosis of TS alone is insufficient to predict the course of ovarian function.

The brief exposure to estradiol valerate requires the onset of breast development to be distinguished from subsequent ovarian function. Treatment was given for 2–3 months and discontinued more than one year before menarche. During that interval, pubertal progression continued without estrogen therapy: she reached Tanner stage IV, had detectable endogenous estradiol and gonadotropin levels that were not frankly hypergonadotropic at age 13 years, and showed uterine growth and endometrial development. This sequence supports the spontaneous nature of menarche.

An FSH level of 22 mIU/mL and AMH level of 0.3 ng/mL during follow-up indicate diminished ovarian reserve despite detectable estradiol and a history of spontaneous menses. Menarche does not ensure sustained gonadal function. In a series of 32 patients with TS and spontaneous menarche, 12 (37.5%) subsequently developed premature ovarian insufficiency; the median age at menopause was 20 years, and the mean interval from menarche to menopause was 5.1 years⁽⁴⁾. Although all patients with structural X-chromosome abnormalities progressed to premature ovarian insufficiency, this subgroup was small.

Follow-up should include menstrual history and serial assessment of gonadotropins and AMH. When fertility preservation is considered, guidelines recommend early counseling and referral to a team experienced in TS¹.

The extent of molecular characterization is a limitation of this case. FISH demonstrates loss of the sequence recognized by the Xp21 probe but does not define the size of the deleted segment or the genes involved. Short stature or ovarian function therefore cannot be attributed to a specific gene. Chromosomal microarray analysis or another higher-resolution method would help delineate the genomic imbalance and refine the breakpoints.

Conclusion

An unbalanced pericentric inversion of the X chromosome, without detectable mosaicism in peripheral blood, does not preclude residual ovarian activity or spontaneous menarche. In this patient, subsequent oligomenorrhea and markers of diminished ovarian reserve show that menarche does not guarantee prolonged preservation of gonadal function. Longitudinal follow-up and cytogenetic characterization are needed to individualize prognosis and reproductive counseling.

Consent for publication

Written informed consent was obtained from the patient for publication of the clinical and cytogenetic information contained in this report.

Conflicts of interest

The author declares no conflicts of interest related to this work.

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