

## Triple X Syndrome

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### Abstract

Triple X syndrome 47XXX is a sex chromosome abnormality characterized by presence of an extra X chromosome. Most of the girls born with triple X chromosomes have no signs or symptoms at birth. The condition often remains undiagnosed until adulthood when the genetic defect is discovered on investigation for other reasons as in this case of a young girl who presented with primary amenorrhoea. Clinical examination was unremarkable and diagnosis was made on chromosomal analysis. She later started having a spontaneous menstrual cycle but prognosis regarding future fertility is guarded.

**Keywords:** Triple X syndrome.

### Introduction

The X chromosome is one of the largest chromosomes and contains hundreds of genes most of which have nothing to do with sex determination. Females normally have two X chromosomes. However, 1 in 1000 apparently a normal female, carries three X chromosomes in the nuclei of body cells.<sup>1</sup> Triple X syndrome results from trisomy (non-disjunction of chromosomes during meiotic divisions of X chromosome). The incidence, like other chromosomal abnormalities increases if mother's age is more than 35 years. The extra X chromosome is very rarely of paternal origin. We document the case of a girl with triple X syndrome who presented with primary amenorrhoea.

### Case Report

A 16 year old girl was seen in the gynaecology clinic for primary amenorrhoea. She was born when her mother was 36 years old. Pregnancy and birth history were unremarkable. Early developmental milestones were age appropriate. She had always been tall for her age, and had gained weight rapidly in the past few years.

At her first visit she was studying in the 9th grade and lived with her parents and three siblings. She was adopted by her maternal uncle in early childhood but was back with her parents after the death of her aunt. She was still very close to her uncle's family. Her academic record was not very good, according to her mother she could not do very well at school despite trying hard. Otherwise she seemed to be of socially acceptable level of intelligence.

Her parents were in their early fifties. Mother was a schoolteacher, had menarche at the age of 12 years. Patient is the youngest of four children, 23 years old elder sisters are twins, and a 19 years old brother. Both her sisters had menarche at about 13 years of age. There was nothing of related significance in her past and family history.

On examination she was 163 cms tall and weighed 60 kg (BMI 22.5). Upper and lower body ratio was 64:99. She had a female phenotype with normal eye span and nasal bridge. Neck was supple without any adenopathy or thyromegaly. Breasts were Tanner Stage III with hypoplastic areola. Axillary and pubic hair were Tanner Stage IV. Abdomen was soft without any palpable mass. External genitalia were normal, labia minora were hypoplastic. Rest of

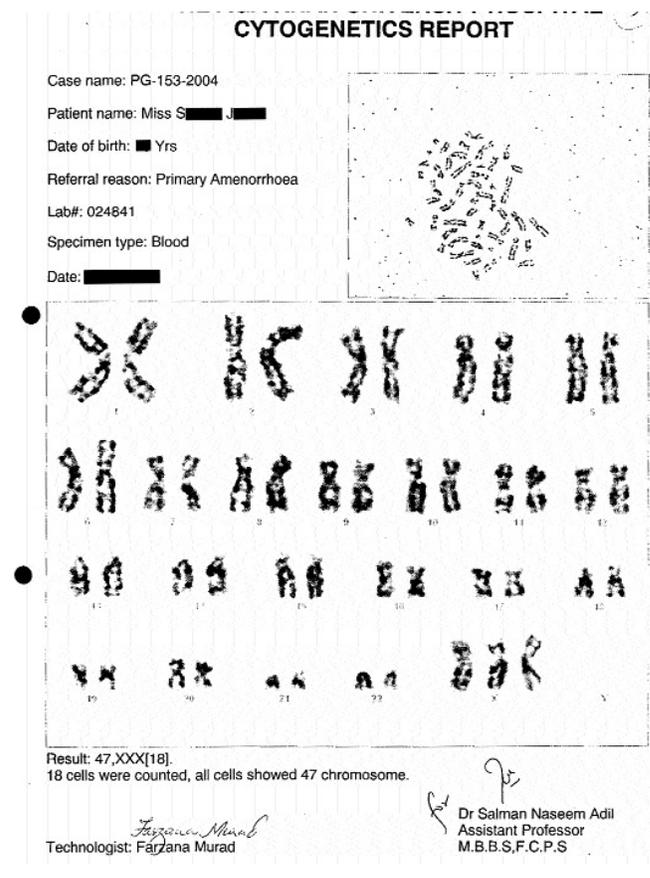


Figure: Cytogenetic study showing 47 XXX chromosomes.

the examination was normal.

Ultrasound scan of pelvis showed uterus slightly smaller than normal (4.2 x 2.6 x 3.4cms), right ovary 2.0 x 1.3 cms and left ovary 2.3 x 1.2 cms.

Her Follide Stimulating Hormone (FSH): 2.24 IU/ml (2 - 13), Leutinizing Hormone (LH): 0.64 IU/ml (0.4-20) and thyroid profile was within normal range. Karyotyping revealed 47, XXX chromosomes (Figure).

A diagnosis of primary amenorrhoea secondary to triple X syndrome was made. The condition was explained to the patient and her mother. An appointment was arranged with the genetic consultant who reassured them regarding her chances of having spontaneous periods and her future fertility.

She returned to the clinic two months later for follow up when she had her first spontaneous menstrual cycle. The cycles were initially irregular but gradually became normal. She is now 21 years old and studying in college.

## Discussion

Triple X syndrome is associated with a vast variation of signs and symptoms. Many affected females are apparently normal and may go unnoticed and undiagnosed.

These females often have a tall stature than their female peers, not explained by parental heights.<sup>3</sup> In addition, in some cases certain physical abnormalities have been reported, such as a relatively small head, vertical skin folds that may cover inner corners of eyes (epicanthal folds), and/or other findings. Structural malformations predominantly related to genitourinary tract have been reported.<sup>4</sup>

Sexual development and fertility are usually normal and several triple X women give birth to chromosomally and physically normal children. Bender et al reviewed 155 cases of triple X syndrome and observed a high prevalence of psychological disturbances but normal phenotype and reproductive competence in the majority of cases.<sup>5</sup> However, some may have fertility problems and recurrent miscarriages. There is a higher incidence of delayed puberty and/or early menopause. Harmon et al.<sup>6</sup> reported that 47 XXX females appeared to experience more reproductive difficulties. On an average they experience more work, social and relationship problems than their siblings. However no difference was found concerning age at first sexual experience, number of marriages, number of pregnancies and number of living children.<sup>6</sup>

Goswami D et al<sup>7</sup> reported two (3.8 %) cases of 47XXX chromosomes among 52 women with premature ovarian failure. Both cases had associated autoimmune thyroid disorder. One of the women with triple XXX syndrome had two pregnancies that were complicated by

premature births and malformation. It has been suggested that testing for thyroid dysfunction, prepregnancy counselling and antenatal screening for foetal malformations are important in women with triple X syndrome. Possible association between triple X and glucose metabolism abnormalities have also been reported.<sup>8</sup> Psychotic illness seems to be more prevalent in triple X adult women than in controls. These disorders respond well to psychotropic drugs.<sup>9</sup>

Affected females typically have normal intelligence but lower IQ than that of their siblings. There may be learning difficulties and they tend to have delayed acquisition of certain motor skills. Rovet J et al<sup>10</sup> compared twelve 47 XXX to sixteen girls with 46XX. Nine of these were siblings of the affected girls. The study evaluated their intelligence through an age appropriate test called the Wechsler intelligence test.<sup>11</sup> Achievement was assessed through a test called The Wide Range Achievement test.<sup>12</sup> They suggested that these females compared to normal girls have reading impairment, poor arithmetic performance and selective disadvantage in verbal ability. They show deficits in verbal comprehension and reasoning. However there is no evidence of increased mental retardation.

Delay of language skills and impaired psychosocial adaptations puts them at risk of being socially isolated. These girls need supportive parents and atmosphere that provides constant stimulation and love for learning and interaction.

## Conclusion

Most children with triple X chromosomes appear physically normal at birth. They are at increased risk for difficulties in language, neuromotor and learning skills and behavioral problems. There is higher incidence of delayed puberty and early menopause and the condition should be kept in mind when investigating such cases. Karyotyping should be part of the workup as it confirms the diagnosis.

## References

1. Duncan SLB. Embryology of the female genital tract: its genetic defects and congenital anomalies. In: Shaw RW, Soutter WP, Stanton SL, editors. Section 1: Basic principles and investigations, Gynaecology. 3rd ed. London: Churchill Livingstone, 2003; pp 1-19.
2. Kotzot D. Abnormal phenotypes in uniparental disomy (UPD): fundamental aspects and critical review with bibliography of UPD other than 15. *Am J Med Genet* 1999; 82: 265-74.
3. Liebezeit BU, Rohrer TR, Singer H, Doerr HG. Tall stature as presenting symptom in a girl with triple X syndrome. *J Pediatr Endocrinol Metab* 2003; 16: 233-5.
4. Hogge WA, Vick DJ, Schnatterly PA, McMillan RH. Bilateral renal agenesis and Mullerian anomalies in a 47, XXX fetus. *Am J Med Genet* 1990; 36: 73-5.
5. Bender BG, Harmon RJ, Linden MG, Bucher-bartelson B, Robinson A. Psychosocial Competence of unselected young adults with sex chromosome abnormalities. *Am J Med Genet* 1999; 88: 200-6.
6. Harmon R, Bender B, Linden M, Robinson A. Transition from adolescence to early adulthood: Adaptation and psychiatric status of women with 47, XXX. *J Am Acad Child Adolesc Psychiatry* 1998; 37: 286-91.
7. Goswami R, Goswami D, Kabra M, Gupta N, Dubey S. Prevalence of the

- triple X syndrome in phenotypically normal women with premature ovarian failure and its association with auto-immune thyroid disorders. *Fertil Steril* 2003; 80: 1052-4.
8. Kanaka-Gantenbein C, Kitsiou S, Mavrou A, Stamoyannou L, Koliaki A, Kekou K, et al. Tall stature, insulin resistance and disturbed behavior in a girl with the Triple X Syndrome harbouring three SHOX genes: Offspring of a father with mosaic Klinefelter Syndrome but with two maternal X chromosomes. *Horm Res* 2004; 61: 206-10.
  9. Otter M, Schrandt-Stumpel CT, Curfs LM. Triple X syndrome: a review of the literature. *Eur J Hum Genet* 2010; 18: 265-71.
  10. Rovet J, Nestley C, Bailey J, Keenan M, Stewart D. Intelligence and achievement in children with extra X aneuploidy: A longitudinal perspective. *Am J Med Genet* 1995; 60: 356-63.
  11. Kaplan RM, Jaccuzo DP. *Psychological Testing: Principles, Application & Issues*. 7th ed. Belmont: California, Thomson Wadsworth, 2009.
  12. Sattler JM. *Assessment of Academic Achievement*. In *Assessment of Children: Behavioral and Clinical Applications*. 4th ed. San Diego: Jerome M Sattler Publisher Inc 2002.
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