A Case Report on Tetrasomy X in a Teenage Girl Presenting with Premature Ovarian Insufficiency

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ABSTRACT

Tetrasomy X (48, XXXX) is an extremely rare sex chromosomal aneuploidy. Very few cases of tetrasomy X with primary ovarian insufficiency have been reported to date, especially from India. The varied heterogeneity of presenting manifestations and also presentation at different ages make diagnosis difficult. Though rare, adolescent case groups make it difficult to accurately diagnose as tetrasomy X. Though rare, cases that presented during adolescence most commonly reported primary or secondary amenorrhea due to primary ovarian insufficiency. Early identification can improve reproductive outcomes as well as the general quality of life through hormone replacement therapy. This current case report describes that of a 16-year-old girl presenting with secondary amenorrhea, poor socio-adaptive functioning, and learning difficulties. Other physical features included ocular hypertelorism, epicanthic folds, a wide nose, and long, slender upper and lower extremities. Secondary sexual characteristics were poorly developed, with absent axillary and pubic hair and infantile external genitalia; however, stage 3 breast development was observed. Imaging studies showed a small uterus and atrophic ovaries. Primary ovarian insufficiency was established by high follicle-stimulating hormone and luteinizing hormone levels. Karyotyping of peripheral lymphocytes by G-banding confirmed tetrasomy X (48, XXXX). Apart from hormone replacement therapy, a multidisciplinary approach for psychosocial rehabilitation was undertaken.

Keywords: Tetrasomy X, 48 XXXX, primary ovarian insufficiency, intellectual disability

INTRODUCTION

Chromosomal aberrations can be classified as numerical or structural. [1,2] Tetrasomy X (48, XXXX) is a rare numerical sex chromosomal aneuploidy and was first described by Carr *et al.* in 1961. [F3] To date, only a few cases have been reported worldwide. Reported cases show[4,5,6] The reported tetrasomy X cases present with varied clinical manifestations, including developmental delays, low IQ scores, delayed puberty, menstrual abnormalities, and secondary amenorrhea. O[5,6,7] On the contrary, other sex chromosomal aneuploidies like 45, X karyotype (Turner syndrome) and 47, XXY karyotype (Klinefelter syndrome) usually have characteristic phenotypic features and are easily recognizable.[8] Hypersomnia, seizure disorders, and craniofacial abnormalities such as epicanthic folds, upward slanting eyes, excess skin at the back of the neck, and widely spaced eyes have also been reported.[8] However, none of these features are specific, highlighting the need for further study and detailed case reports. Most tetrasomy X case reports involve younger girls, with mental retardation as the common indication for karyotyping. Adolescent cases mostly present with this, underscoring the need for further study and detailed case reporting of this condition. The case reports on tetrasomy X are about relatively younger girls, and the commonest indication for advising karyotyping in tetrasomy X cases is mentioned in different published case reports as mental retardation. Cases presented in adolescent age groups are mostly due to menstrual abnormalities like primary or secondary amenorrhea. Half of the adolescent girls have reported having normal pubertal development, whereas the rest showed delayed puberty or development of secondary amenorrhea following normal puberty due to primary ovarian insufficiency. 5, 7 The scarcity of reported cases of tetrasomy X in the literature makes it difficult to establish the true frequency of primary ovarian insufficiency. Reproductive outcomes in women with tetrasomy X vary widely. Although among them. [6, 10] The reproductive outcomes in women with tetrasomy X are highly variable. Hypersomnia, seizure disorders, and craniofacial abnormalities like epicanthic folds, upward slanting eyes, excess skin at the back of the neck, and

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widely spaced eyes have also been reported.9 However, none of these features are specific, which stresses the necessity for additional study and detailed case reporting of this condition. Though the possibility of having babies in women with tetrasomy X is quite rare, some women with tetrasomy X have also reported having normal babies with 46 chromosomes. In the published literature, we came to know about a woman with tetrasomy X who had a normal chromosomal baby and another with a Down syndrome baby. Another woman had reported having a baby with omphalocele. These observations are insufficient to draw conclusions. However, this observation is not sufficient to draw any definite conclusion about the pregnancy outcomes and fetal risks. Early potential fetal risks in the offspring of tetrasomy X.[7] Furthermore, early initiation of hormone replacement therapy may control the long-term health effects of primary insufficiency, like osteoporosis. Therefore, early identification and timely management of tetrasomy X cases, along with timely initiation of multidisciplinary therapy, can significantly improve quality of life. of these individuals.

Clinical history

A 16-year-old girl attended the gynecology outpatient clinic with her mother, complaining of amenorrhea for the past two years. She had menarche at 14 years and no further menstrual bleeding thereafter. Her mother reported academic difficulties and that she had not attended school for two years due to learning difficulties. The mother was 28 years old and was having difficulty coping with academic activities and noted that, due to learning difficulties, she had not attended school for the past two years. The mother was 28 years old at the time of delivery. Neither parent had reported any significant medical or surgical history, and there was no consanguinity. T among parents. As the pregnancy was unplanned, the mother took some medications for abortion, but when they failed, she continued the pregnancy. Her antenatal period was uneventful. She was delivered at term by normal vaginal delivery at home. The girl did not cry immediately after birth and was admitted to the nearby government hospital when she did not pass meconium within the first 24 hours. She weighed 2700 g at birth. Her developmental milestones were delayed, and she started speaking at around age 5. At 5 years of age. The parents noticed learning difficulties when she began attending school. She had no history of convulsions. She also exhibited poor social and communication skills, with frequent irritability and anger. She has a 21-year-old sister with issues. She has an elder sister, 21 years of age, who is studying in college, has a good academic record, and has a normal menstrual history.

Physical examination revealed epicanthic folds, long philtrum, high-arched palate, facial asymmetry, depressed nasal bridge, broad nose, widely spaced eyes, short webbed neck, and low posterior hairline. She also had mild scoliosis, and her upper and lower extremities were relatively longer with broad wrists. She was 168.2 cm tall and weighed 62.5 kg, both at the 75th percentile. She had Tanner I pubic hair and Tanner 3 breast development. On auscultation, no abnormal heart sounds or murmur were identified. A clinical psychologist assessed her socio-adaptive functioning with the Vineland Social Maturity Scale (VSMS). Her social age was 8 years 8 months, and the calculated Social Quotient was 57, denoting a mild deficit in socio-adaptive functioning. In the sub-domains, she scored very low in social-help general, with an age equivalent of 4 years 4 months; self-help eating, 9 years 4 months; self-help dressing, 6 years 8 months; self-direction, 11 years 4 months; occupation, 11 years 4 months; communication, 8 years 8 months; locomotion, 6 years; and socialization, 6 years 4 months.

Laboratory investigation revealed a very high follicle-stimulating hormone (FSH) level of 104.7 mIU/mL (normal range 3.0-22.0 mIU/mL), luteinizing hormone (LH) level of 63.1 mIU/mL (normal range 2.0-11.0 mIU/mL), and an estradiol level of 23 pg/mL (normal range: 24- 400 pg/mL). Magnetic resonance imaging (MRI) of the pelvis revealed a small uterus (measuring 38×11×20 mm) with atrophic ovaries. The biochemical and radiological investigation points toward primary ovarian insufficiency. The patient's history of developmental delay, poor intellectual functioning, relatively tall stature, underdeveloped secondary sexual characteristics, and the hormonal and radiological findings involving reproductive organs raised a strong suspicion of an underlying chromosomal abnormality. Considering the overall clinical presentation and investigation findings, karyotyping was performed to establish the diagnosis. Karyotyping was performed from peripheral blood lymphocytes by GTG banding, disclosing a karyotype of 48, XXXX.

After confirmation of the diagnosis, estrogen therapy was initiated, and the parents were guided to a special school, with a learning disability certificate issued by the clinical psychologist. Monthly follow-up was also advised.

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DISCUSSION

The adolescent girl presented with complaints of secondary amenorrhea, having had only a single episode of menstrual bleeding at age 14. Her secondary sexual characteristics were poorly developed, and she additionally showed several physical features associated with low socio-adaptive performance and learning difficulties. Karyotyping confirmed tetrasomy X (48, XXXX) — a rare chromosomal aneuploidy that, when accompanied by premature ovarian failure (POF), has been documented in only a handful of case reports. [5,9] Hossain et al. described a young woman with tetrasomy X who presented with unusually tall stature (194 cm), discordant secondary sexual development — breast development at Tanner stage B4 alongside pubic hair at stage P1 — and hypergonadotrophic hypogonadism. Similarly, Rooman et al.[5] reported a 19-year-old girl with tall stature (181.8 cm) and primary ovarian failure. Most of these features were mirrored in our patient, underscoring the phenotypic overlap between the two cases. A further case of POF associated with mosaic pentasomy/tetrasomy X was reported by Wood et al.[10] The underlying mechanisms of tetrasomy X also appear to vary: some studies describe uniparental maternal tetrasomy X,[11] while others report three maternally derived X chromosomes with one paternal X, or polysomy rescue.[12]

Tall stature in tetrasomy X has often been attributed to the presence of two extra X chromosomes, since the SHOX (Short Stature Homeobox) gene — located at the tip of the short arm of the X chromosome — plays a central role in linear growth. Notably, this growth acceleration tends to become more pronounced later in childhood and adolescence rather than at birth.[13]

This variability is echoed in a series of four cases reported from China[13] that are phenotypically female and range in age from 2 to 14 years. Each of these patients shared intellectual disability, learning difficulties, and impaired language and recall abilities — findings that were likewise present in our patient, and that appear to hold consistently across childhood, adolescence, and young adulthood in tetrasomy X. Beyond these core features, though, the presentations diverged: three of the four had ocular hypertelorism and epicanthic folds, two had mild jaw prognathism and cleft palate, and the 14-year-old girl specifically showed a depressed nasal bridge and small palpebral fissures. Two patients, aged 8 and 14, had short bilateral pinkies, while one additionally had polydactyly and another clinodactyly of the fingers and toes. Reproductive anomalies were also noted — an 8-year-old with naïve vulvar findings and possible uterine agenesis, and a 5-year-old with an immature uterus and ovaries — alongside patent ductus arteriosus in three of the four. Taken together with our case, these reports point to marked phenotypic variability in tetrasomy X: developmental delay, learning difficulties, and gonadal dysfunction recur fairly consistently, whereas features like seizure disorders and hypersomnia are inconsistent and clearly not universal.

Hormonal work-up in our patient revealed markedly elevated FSH and LH, and she had already developed osteoporosis by the time of presentation — a consequence, most likely, of prolonged estrogen deficiency going unaddressed due to late diagnosis. This reinforces the importance of early recognition and timely initiation of hormone replacement therapy, particularly since several reported cases have presented earlier, even before the onset of menstruation. Jayaraman et al.[14] described a 17-year-old with tetrasomy X presenting with hypersomnia, along with dysmorphic features including an elongated face and bilateral single palmar creases; her BMI sat at the 88th percentile, and she had an associated ventricular septal defect, though menstrual history and uterine/ovarian imaging were not documented in that study. Our patient, by contrast, had a normal sleep pattern throughout. Kristesashvili et al.[6] reported a 17-year-old with primary ovarian insufficiency accompanied by psychomotor retardation and developmental delay; she had reached menarche at 13 and experienced three menstrual episodes before developing secondary amenorrhea, with normal external genitalia and female-pattern pubic hair. Collectively, these cases reinforce how variably tetrasomy X can present phenotypically.

Given this variability, even a subtle presentation of early POF alongside learning disability warrants a high index of suspicion.

With timely recognition and coordinated multidisciplinary care, individuals with tetrasomy X can go on to lead largely normal lives and participate fully as members of society. Management should be tailored to their learning needs, incorporating appropriate educational and occupational guidance, along with hormone replacement therapy and nutritional supplementation (calcium and vitamin D) as core components of care. Because cardiac

structural defects can co-occur, an early echocardiogram is advisable, and clinicians should also remain alert to associated renal and dental issues, as well as a heightened susceptibility to infections. Equally important is engaging and educating the family, so they are equipped to support the child through these various challenges. Ultimately, a high index of suspicion, coupled with early recognition and multidisciplinary management, offers the best path to a normal life for individuals with tetrasomy X.

With early recognition and multidisciplinary management, these individuals may lead an almost normal life and be useful members of society. Management would include education and occupational guidance as per their learning abilities. Hormone replacement and nutritional supplements (Calcium and Vit D) form an important part of the management. Some of these individuals may also have cardiac structural defects, which would necessitate an early echocardiogram and appropriate management. Besides, these girls may have renal and dental problems. They are also prone to frequent infections. The family needs to be made aware of, and guided in dealing with these issues to ensure holistic care. A high degree of suspicion, early recognition, and multidisciplinary care will ensure a normal life for people with tetrasomy X

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CONCLUSION

Due to the absence of consistent physical anomalies, it is difficult to identify the tetrasomy X cases with only phenotypic characteristics. However, primary ovarian failure with psychomotor retardation can give some clues regarding possible tetrasomy X, and thus, karyotyping should be considered in these presentations. More case reporting will help identify a syndromic pattern for early detection and prompt diagnosis. A multidisciplinary approach is needed to ensure holistic care and ensure that these individuals can lead normal lives and be useful members of society.

Declaration of conflict of interest: nil

Informed consent:

Written informed consent has been obtained from the parents for disclosure of clinical information and investigations maintain the confidentiality.

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