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Clinical and cytogenetic characteristics of patients with Triple X syndrome: Experience from a tertiary center

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Abstract

Background: Triple X syndrome is the most common sex chromosome aneuploidy in females; however, due to the subtlety of clinical findings, only a small proportion of affected individuals are diagnosed. This study presents the demographic, clinical, and cytogenetic characteristics of patients with Triple X syndrome followed at a single center.

Methods: We retrospectively reviewed the medical records of patients diagnosed with Triple X syndrome at our department between 2008 and 2025. Demographic characteristics, clinical findings including anthropometric measurements, dysmorphic features, associated anomalies, endocrine and neurodevelopmental findings, and cytogenetic results were analyzed.

Results: The study included a total of 20 patients diagnosed with Triple X syndrome, 13 of whom (65%) had a non-mosaic 47,XXX karyotype and 7 (35%) had mosaic chromosomal abnormalities. Four patients received a prenatal diagnosis, four were diagnosed in adulthood, and the remaining patients were diagnosed during childhood. Dysmorphic features; neurodevelopmental problems such as developmental delay, intellectual disability, and attention-deficit/ hyperactivity disorder; as well as cardiac defects and endocrine disorders were the main characteristics observed in the patients.

Conclusion: Triple X syndrome is a relatively common chromosomal disorder, which should be considered in patients who experience congenital anomalies, neurodevelopmental abnormalities, and reproductive problems. Variable and subtle findings should be carefully considered, bearing in mind that mosaic cases may present with diverse and overlapping phenotypes.

Keywords: Triple X syndrome, 47,XXX, sex chromosome aneuploidy, chromosome analysis

Introduction

Triple X syndrome (47,XXX) was first described in 1959 in a female patient presenting with absence of secondary sexual characteristics and primary ovarian failure, and was introduced as the third identified sex-chromosome abnormality, termed 'super-female', with the initial assumption that its manifestations were limited to the genital tract [1]. The incidence of this disorder has been estimated at about 1 per 1,000 females [2].

While the vast majority of patients do not exhibit significant phenotypic abnormalities or marked neurodevelopmental delay, the clinical spectrum is broad, with substantial variability in both manifestations and severity among individuals. Tall stature, minor dysmorphic features, congenital anomalies such as genitourinary malformations, and premature ovarian failure are among the commonly observed findings in affected individuals [2]. Neurodevelopmental problems are also frequently reported in this syndrome [2].

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The condition results primarily from nondisjunction occurring during maternal meiosis, predominantly during meiosis I [3]. The phenotypic features in affected individuals are thought to result from overexpression of genes that escape X-inactivation. Although 47,XXX is the most common karyotype, approximately 10% of patients exhibit mosaicism due to mitotic nondisjunction, which may occur in various karyotypic combinations such as 46,XX/47,XXX, 47,XXX/48,XXXX, or 45,X/47,XXX [4].

In this study, we aimed to systematically evaluate the demographic, clinical, and cytogenetic features of patients diagnosed with Triple X syndrome and followed in our department between 2008 and 2025, and to compare our findings with those reported in the literature.

Methods

The patient registry of the Department of Pediatric Genetics at Hacettepe University Faculty of Medicine was retrospectively reviewed to identify cases diagnosed with Triple X syndrome between 2008 and 2025. Patients with a confirmed cytogenetic diagnosis of Triple X syndrome, including both non-mosaic and mosaic karyotypes, were included in the study.

Patients were evaluated with respect to their presenting complaints, indications for chromosomal analysis, and the diagnostic methods used, including conventional karyotype analysis and chromosomal microarray analysis. Cytogenetic data, including karyotype results and the mosaicism status, were retrieved from laboratory records. Demographic data, including age at diagnosis, current age, parental consanguinity, and maternal and paternal ages at the time of birth, were recorded. Prenatal findings, birth characteristics, and anthropometric measurements at birth and at the time of presentation were evaluated. Clinical features, dysmorphic characteristics, neurodevelopmental findings, associated congenital anomalies, endocrine disorders, visual and hearing assessments, and the presence of comorbidities were also assessed.

Conventional G-banded karyotype analysis was performed on peripheral blood lymphocytes for cytogenetic diagnosis and karyotypes were reported in accordance with the International System for Human Cytogenomic Nomenclature (ISCN) [5]. Chromosomal microarray analysis was conducted using the Thermo Fisher Applied Biosystems CytoScan Optima oligonucleotide array (Thermo Fisher Scientific, Waltham, MA, USA), and data were analyzed with Chromosome Analysis Suite (ChAS) software, version 4.4.

Ethical approval for the study was obtained from the Hacettepe University Ethics Committee (SBA 25/906).

Results

A total of 20 patients diagnosed with Triple X syndrome were included in the study; 13 (65%) had a non-mosaic 47,XXX karyotype, while 7 (35%) had mosaic chromosomal constitutions. Among the mosaic cases, five had a 46,XX/47,XXX karyotype, and two had mosaic karyotypes including Turner syndrome cell lines 45,X/47,XXX. All patients underwent chromosomal analysis, with two patients diagnosed by chromosomal microarray analysis followed by karyotyping. One of the patients evaluated by chromosomal microarray analysis had a 47,XXX karyotype, while the other had mosaic 45,X/47,XXX.

Four patients received a prenatal diagnosis, whereas four others were diagnosed in adulthood. One patient was referred during the prenatal period, while the others presented postnatally. The indications for prenatal diagnosis were increased risk on prenatal screening tests and advanced maternal age. The age at initial evaluation ranged from 1 day to 48 years, with a mean age of 10.8 years. Among the 16 patients diagnosed postnatally, the mean age at diagnosis was 11.5 years (range: 1.5 months–48 years). One patient died at 2.5 months of age due to congenital heart disease; the mean current age of the remaining patients was 19.5 years, ranging from 3.2 to 58 years. The mean maternal and paternal ages at delivery were 32.3 and 36.3 years, respectively. Parental consanguinity was present in five families. A history of preterm birth was present in three patients.

One of the patients with Turner syndrome cell lines (45,X/47,XXX) was referred due to critical aortic stenosis with endocardial fibroelastosis, whereas the other presented with short stature. Among the patients diagnosed during childhood, the most common reasons for referral were growth retardation, developmental delay, and dysmorphic features. Among the four women who presented in adulthood, the reasons for

referral included having a child with a chromosomal abnormality, recurrent pregnancy loss, and premature ovarian insufficiency in two patients.

The mean height, weight, and head circumference SDS values at presentation among patients diagnosed during childhood were −1.19, −1.06, and −0.92, respectively. Dysmorphic features were present in 94.1% of patients with available data, and the most common findings are summarized in Table 1. Developmental delay was observed in seven patients, three of whom were born prematurely at 26, 29, and 32 weeks of gestation. Among these preterm patients, one born at 29 weeks was diagnosed with autism and another born at 32 weeks developed seizures; however, their cognitive levels could not be objectively assessed. Among the remaining patients, two had borderline intellectual functioning, one had mild intellectual disability, and one had moderate intellectual disability. Attention-deficit/hyperactivity disorder (ADHD) was identified in two patients, and a history of febrile seizures was noted in one patient. Cranial MRI of one patient with a history of preterm birth revealed extensive areas with encephalomalacia and reduced parenchymal volume. No significant central nervous system abnormalities were observed in the other patients who underwent MRI. Among endocrine disorders, hypothyroidism was identified in four patients and adrenal insufficiency in two patients, with one patient affected by both conditions; premature ovarian failure (POF) was observed in two patients. As additional comorbidities, hypogammaglobulinemia was observed in two patients and a history of hematuria was noted in two patients. The demographic characteristics, anthropometric measurements, and systemic findings of the patients are summarized in Table 1.

Table 1. Demographic, anthropometric, and clinical characteristics of the patients

Characteristic	Value
Demographic characteristics	
Age at referral (years)	Mean 10.8 (range prenatal–48 years)
Age at diagnosis (years)	Mean 11.5 (range prenatal–48 years)
Current age (years)	Mean 19.5 (range 3.2–58)
Maternal age at delivery (years)	Mean 32.3 (range 22–46)
Paternal age at delivery (years)	Mean 36.3 (range 26–53)
Parental consanguinity	5/20 (25%)
Anthropometric measurements	
Birth weight	2.6 kg (range: 955–3,570 g)
Height SDS	−1.19 ± 1.55
Weight SDS	−1.06 ± 1.41
Head circumference SDS	−0.92 ± 1.50
Dysmorphic features	
Epicanthal folds	6/17 (35.3%)
Hypertelorism	4/17 (23.5%)
Upslanting palpebral fissures	2/17 (11.7%)
Clinodactyly	4/17 (23.5%)
Pectus deformity	2/17 (11.7%)
Scoliosis	3/17 (17.6%)
Developmental delay	7/16 (43.7%)
Cognitive impairment	4/7 (57.1%)
Endocrine problems	7/13 (53.8%)
Congenital heart disease	7/13 (53.8%)
Visual problems	3/11 (27.2%)
Hearing loss	3/11 (27.2%)

Discussion

Triple X syndrome is the most prevalent sex chromosome aneuploidy in females. However, it is estimated that only approximately 10% of patients with Triple X syndrome are diagnosed, as most do not present with clearly recognizable dysmorphic features at birth that would prompt clinical suspicion [3,6]. The rate of prenatal diagnosis has increased with the widespread use of non-invasive prenatal testing (NIPT). In our cohort, there were no patients diagnosed through NIPT; however, as NIPT is increasingly adopted in our country, the rate of incidentally diagnosed patients is likely to increase.

In the postnatal period, diagnosis is usually established through chromosome analysis performed for hypotonia, developmental delay, or minor dysmorphic features [3]. In a large cohort study including 74 cases, 44 diagnosed prenatally and 30 postnatally, medical outcomes were shown to be more favorable in the prenatally diagnosed group [4]. However, this difference was suggested to reflect the fact that postnatal diagnoses are typically made based on medical indications such as developmental delay, unlike the largely incidental nature

of prenatal detection. In our cohort, the indications for postnatal chromosome analysis were consistent with the literature; however, among the patients diagnosed prenatally, one showed normal development, one had intellectual disability, one had ADHD, and one with mosaic 46,XX/47,XXX exhibited motor developmental delay.

In Triple X syndrome, the mean maternal age at delivery is reported to be approximately 33 years, and affected newborns tend to have birth weights 400–500 g lower than average, yet they generally present with a normal appearance at birth [2]. In our study, the mean maternal age was found to be similar (32.3 years), but the relatively lower birth weight observed in our cohort was thought to be attributable to patients with a history of premature birth.

In childhood, accelerated linear growth has been reported, with average height typically exceeding the 75th percentile [2]. Although it has been suggested that Triple X syndrome should be considered in the evaluation of females with tall stature, individuals with short stature have also been reported [3,7]. In terms of body proportions, the extremities tend to be relatively long. The mean height SDS in our cohort was −1.19, which is lower than expected. Our cohort may be subject to ascertainment bias, as it primarily included patients referred postnatally due to growth retardation and endocrine disorders, as well as individuals with mosaic karyotypes including 45,X/47,XXX. Therefore, it should be kept in mind that considerable phenotypic variability exists among patients with Triple X syndrome, and tall stature is not a universal feature, particularly in those with mosaic karyotypes including a 45,X cell line.

Clinodactyly and epicanthal folds are the most common minor dysmorphic features reported [2,3]. Although prominent dysmorphic features are not typically expected in affected individuals, other reported findings include hypertelorism, upslanting palpebral fissures, high-arched palate, pes planus, pectus excavatum, kyphoscoliosis, and joint hyperextensibility [3,4]. Although our patients did not exhibit a typical facial gestalt, minor dysmorphic features consistent with those reported in the literature were observed (Table 1).

Congenital anomalies such as cleft lip or palate, cardiac defects, and genitourinary abnormalities may accompany the condition [3,4]. Additional reported features comprise gastrointestinal complaints, including gastroesophageal reflux, constipation, and abdominal pain, as well as neurological symptoms such as seizures, headaches, and tremor, and various ophthalmologic and dental problems [3,4]. The most frequently observed congenital anomaly in our cohort was congenital heart disease.

Sex chromosome aneuploidies are known to be associated with neurodevelopmental problems. In the presence of an additional sex chromosome, such as triple X syndrome, increased rates of autism and social anxiety have been reported; however, when interpreting these elevated risks, ascertainment bias must be taken into account [8]. Moreover, it has been reported that the same aneuploidy can manifest with markedly different phenotypes even within the same family [8]. In affected females, a mean reduction of approximately 20 points in overall intelligence quotient (IQ) has been observed, with both verbal and performance IQ being affected; however, deficits in verbal IQ are significantly more pronounced [7]. In addition, attention deficit, learning difficulties, delayed motor development, speech and language impairments, behavioral problems, and a range of psychiatric disorders, including depression, anxiety, and psychotic disorders, have been reported [7,8]. In line with the literature, several patients in our cohort exhibited neurodevelopmental and neuropsychiatric findings, including developmental delay, intellectual disability, learning disabilities, ADHD, and anxiety; however, only one patient had a diagnosis of epilepsy. Notably, three of the patients with neurodevelopmental impairment had a history of prematurity, and the patient with seizures was also born prematurely.

Auditory processing disorders, which may contribute to delayed language development, have been described in affected patients, whereas hearing loss is not considered a commonly reported feature [2]. In our cohort, hearing loss was identified in three patients. Similarly, although ophthalmological anomalies are not among the typical features associated with the syndrome, case reports have been reported involving ocular pathologies such as high myopia and chorioretinal coloboma [9,10]. In our cohort, two patients had refractive errors, and in one patient with a history of premature birth, absent bilateral responses were observed on visual evoked potentials, while electroretinography revealed bilaterally delayed latency responses.

Although most women with Triple X syndrome exhibit normal reproductive function, an increased frequency

of POF has been reported, and 3.8% of women with POF have been found to have Triple X syndrome [11]. In our cohort, two of the patients who presented in adulthood were referred due to POF; however, this proportion may increase with advancing age. In addition, while hypothyroidism is not considered a common finding among other endocrine problems, autoimmune thyroid disorders have been reported in patients with Triple X syndrome [12]. Adrenal insufficiency has also been reported and was described as coincidentally occurring with congenital adrenal hyperplasia [13]. In our cohort, hypothyroidism was observed in a total of four patients; one patient had Hashimoto thyroiditis, and another patient exhibited central hypothyroidism accompanied by central adrenal insufficiency; however, further molecular investigations to evaluate a hypopituitarism etiology could not be performed. The other patient suspected of having adrenal insufficiency had a mosaic 45,X/47,XXX karyotype and underwent surgery for critical aortic stenosis.

The main limitation of this study is the insufficient sample size of the patient groups, preventing comparative analyses among patients with different chromosomal constitutions.

In conclusion, given that Triple X syndrome is a relatively common chromosomal disorder, it should be considered in patients presenting with congenital anomalies and neurodevelopmental problems in childhood, and particularly in patients with reproductive issues in adulthood. The significant clinical variability observed in our cohort further underscores the importance of considering this condition to prevent delayed diagnosis.

Author contribution

Conception and design: G.Ü.D., G.E.U., P.Ö.Ş.K.; Data acquisition: N.B.A.; Data analysis: G.Ü.D., N.B.A., P.Ö.Ş.K.; Data interpretation: G.Ü.D., N.B.A., P.Ö.Ş.K.; Drafting of the manuscript: G.Ü.D.; Critical revision of the manuscript: G.Ü.D., N.B.A., G.E.U., P.Ö.Ş.K. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Ethics Committee (Date: November 17, 2025, Decision/ Protocol No: SBA 25/906). Ethics committee approval and informed consent were not required for this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study..

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