

ORIGINAL
INVESTIGATION

Clinical and Cytogenetic Evaluations of Patients with Turner Syndrome: Are We Aware Enough?

Semra Gürsoy¹, Özge Aksel Kılıçarslan², Özlem Giray Bozkaya¹, Elçin Bora², Nurettin Ünal³, Derya Erçal¹

ABSTRACT

Objective: The objective of the present study was to describe the phenotypic features of Turner syndrome (TS) and to investigate the relationship between the genotype and the phenotype.

Materials and Methods: We studied 26 female patients who were enrolled between 2006 and 2015. Physical features, clinical history, laboratory findings, and imaging test results were recorded. Chromosomal analysis was performed on peripheral blood lymphocyte cultures of the patients.

Results: The mean age of the study population was 10.4±5.6 years (range, 1 day to 17 years). Three patients were diagnosed in the neonatal period. Although the most common phenotypic feature was short stature (92.3%), the characteristic stigmata were usually seen in the 45, X karyotype. Among the 26 patients, monosomy 45, X was detected in 7 (26.9%) of them. Eleven percent of our patients had 46,X,i(X) (isochromosome Xq), while the rest demonstrated mosaic karyotypes [45,X/46,XY (19.2%); 45,X/46,XX (11.5%); 45,X/46,X,i(X) (11.5%); 45,X/46,XX,r(X) (7.7%); 45,X/46,X,i(Y) (3.8%); 45,X/47,XXX (3.8%); and 45,X/46,XX del(Xp) (3.8%)].

Conclusion: TS is one of the most common sex chromosome abnormalities, but it is frequently underdiagnosed. The frequency of the monosomy 45, X karyotype in TS is less than previously thought. Therefore, patients should be evaluated by chromosome analysis in case there is clinical suspicion.

Keywords: Turner syndrome, ring X chromosome, isochromosome, mosaicism, short stature

INTRODUCTION

Turner syndrome (TS) is one of the most common sex chromosome abnormalities that is usually caused by loss of a part or the entire X chromosome. It occurs in approximately 1/2500 live-born females (1). The true prevalence of TS is uncertain as the patients with mild phenotypic features may remain undiagnosed. Many of the TS cases previously described are characterized by variable phenotypes. The main abnormalities in TS are short stature, primary amenorrhea, infertility, and characteristic stigmata. Edema of the hands or feet in the neonatal period, nuchal folds, a webbed neck, a low posterior hairline, cubitus valgus, a short fourth metacarpal, multiple pigmented nevi, and nail hypoplasia are usually present in TS. Furthermore, heart defects, kidney malformations, hypothyroidism, visual and hearing defects, and gastrointestinal disorders are other potential abnormalities (2).

The 45, X karyotype is observed in 1% to 2% of conceptuses, 10% of miscarriages, and 1% of stillbirths. More than 99% of 45, X conceptuses result in spontaneous loss, usually before 28 weeks. The reason why 1% survive to term with relatively minor somatic abnormalities is unknown, although it has been hypothesized that this is due to undetected mosaicism for a cell line with the entire or a part of the second sex chromosome (3, 4).

Although approximately 50% of affected individuals have the 45, X karyotype and 20% to 30% have mosaicism (45, X and at least one other cell line), the rest have various structural abnormalities (5). The more frequent of these structural abnormalities include the presence of an isochromosome of the long arm of the chromosome X [i(Xq)], ring X, and mosaicism for two or more normal or abnormal cell lines (45,X/46,XX; 45X/46,X,i(Xq); or 45,X/46,XY). On the other hand, TS may be mosaic for a triple X (47/XXX) cell line (5). Clinical stigmata, except short stature, are usually inconsistent, and the physical manifestations of TS largely depend on the karyotype (7). Here we present the genotypic and phenotypic features of patients with TS diagnosed in our department.

MATERIALS and METHODS

This retrospective and observational study included 26 female patients who were enrolled from the Department of Pediatric Genetics of Dokuz Eylul University Medical School, İzmir, Turkey between Ocak 2006 and November 2015. All these patients were referred to us due to the presence of several clinical features including short stature, TS stigmata, and

¹Department of Pediatric Genetics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

²Department of Medical Genetics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

³Department of Pediatric Cardiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

Submitted
24.12.2015

Accepted
16.05.2016

Correspondence

Semra Gürsoy,
Department of Pediatric Genetics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey
Phone: +90 (232) 412 22 22
e.mail:
dr.semra@hotmail.com

Table 1. Distribution of cytogenetic analysis of 26 patients

Karyotype Group	Karyotype Patients	No. Of (%)
Classic Turner Syndrome (26.9%)	45,X	7 (26.9%)
	45,X/46,XY	5 (19.2%)
	45,X/46,XX	3 (11.5%)
Others (73.1%)	46,X,i(X)	3 (11.5%)
	45,X/46,X,i(X)	3 (11.5%)
	45,X/46,XX,r(X)	2 (7.7%)
	45,X/46,X,i(Y)	1 (3.8%)
	45,X/47,XXX	1 (3.8%)
	45,X/46,XX del(Xp)	1 (3.8%)

Table 2. Clinical features of the patients

Clinical features	Group 1 Classic monosomy (n: 7)	Group 2 Other karyotypes (n: 19)
Short stature	5 (71%)	19 (100%)
TS stigmata		
Webbed neck	3 (42.8%)	1 (5.2%)
Low posterior hairline	2 (28.5%)	3 (15.7%)
Cubitus valgus	1 (14.2%)	6 (31.5%)
Widely spaced nipples	4 (57.1%)	7 (36.8%)
Short fourth metacarpal	1 (14.2%)	2 (10.5%)
Edema of the hands/feet	1 (14.2%)	1 (5.2%)
Cardiovascular findings	1 (5) (20%)	3 (11) (27.2%)
Renal findings	0 (6)	3 (15) (20%)
Endocrine findings	0 (6)	3 (16) (18.7%)
Ear findings	2 (28.5%)	0
Diagnosis in the neonatal period	2 (28.5%)	1 (5.2%)
Primary amenorrhea*	1 (14.2%)	4 (21%)
Intellectual disability	0	1 (5.2%)
Brain abnormalities	1 (14.2%)	0

* Absence of menses at the age of 16 years when secondary sexual characteristics are present or absence of menses at the age of 14 years when secondary sexual characteristics are not present
TS: Turner syndrome

primary or secondary amenorrhea. The study included 2 groups: group 1 with classic monosomy and group 2 with other karyotypes. Physical features, clinical history, laboratory findings such as thyroid markers and celiac antibodies, and imaging test results were recorded. Patients with speech impairment were evaluated with hearing tests.

All patients provided written informed consent for cytogenetic testing. Chromosome preparations were obtained from lymphocyte cultures, and G banding was performed to identify individual chro-

Table 3. Clinical and cytogenetic findings in TS patients diagnosed in the neonatal period

Patient No.	Karyotype	Reason for admission	Edema of the hands or feet	Hearing loss
Patient 1	45,X	Prenatal karyotype was 45,X	-	+
Patient 2	45,X/46,XX,del (Xp)	Intrauterine growth retardation	+	-
Patient 3	45,X	Corpus callosum agenesis	+	-

TS: Turner syndrome

mosomes. Karyotyping was performed according to guidelines of the International System for Human Cytogenetic Nomenclature. At least 25 metaphases were studied for karyotyping. In case of suspected mosaicism, 100 cells were counted. The study was performed in accordance with the Helsinki declaration.

RESULTS

Twenty-six patients with a suspicion of TS were identified between 2006 and 2015. The most common karyotype was 45, X (n=7, 26.9%), classic monosomy, which we named it as group 1. In the other group, group 2, which had the patients with other karyotypes, 11 % of our patients had 46, X, i(X) (isochromosome Xq), while the rest demonstrated mosaic karyotypes (61.6%). The detailed description of patient karyotypes are shown in Table 1.

The mean age of the study population was 10.4±5.6 years (range, 1 day to 17 years), and the mean age of the patients with the group 1 and other karyotypes group 2 at the time of the initial diagnosis was 8.4±7.1 years and 11.2±5 years, respectively. Short stature was the cardinal phenotypic feature and was detected in 92.3% of the patients. Five patients were referred to us for primary amenorrhea, and four of them had Y-chromosome abnormalities. The characteristic features of TS were usually present in monosomy X patients (Table 2).

Abdominal ultrasonography was performed in all patients. One of them (mosaic karyotype) had simple renal cortical cysts, whereas two other patients (one of them had a mosaic karyotype while the other had isochromosome X) had horseshoe kidney. Hearing loss was found in two patients who had both 45, X monosomy. Two patients had hypothyroidism and celiac disease at the time of the diagnosis, whereas another patient had only hypothyroidism. Echocardiography was performed in 16 patients. Patent ductus arteriosus was observed in a single patient with classical monosomy, and mitral insufficiency was detected in two with mosaic karyotypes and left ventricular hypertrophy in one with isochromosome X. Mosaicism with 46,XY or other Y-chromosome abnormalities were demonstrated in six patients (23%) in whom the most frequent cause of hospital admission was primary amenorrhea. One patient with the 45, X karyotype, had short 1., 4., and 5. metatarsals. Intellectual disability was detected in a single patient who had the 45, X/47, XXX karyotype. Three patients were diagnosed in the neonatal period, and the characteristic features of these patients are summarized in Table 3.

DISCUSSION

Turner syndrome is the consequence of the complete or partial absence of one X chromosome in a female with short stature and gonadal dysgenesis. Approximately 45% of postnatal TS patients have a pure 45, X cell line without any detectable mosaicism (8). However, due to the results of new studies, classic monosomy was observed with gradually decreasing rates. In 2014, Al Alwan et al. (9) reported classic monosomy in 16 (31%) of 52 patients. In our study, 26.9% of the patients had the 45, X karyotype and the rest had mosaicism or other X-chromosome abnormalities; the frequency of classic monosomy is less than that in reported data in current literature. This is most probably because every patient with a clinical suspicion of TS underwent 100 metaphase cell evaluation in karyotype analysis, leading to increased rates of the mosaic karyotype. We need to keep in mind that milder phenotypic features can be detected in patients with mosaic karyotypes and that this type of TS is much more common than expected.

Other karyotypes that may be mosaic with 45,X most commonly include the following: 46, X, i(Xq); 46,XX; 46,XY; 47,XXX; or 46,X,del(Xp). Typically, the isochromosome of the X, consisting of two long arms of the X chromosome, is the most frequent mosaic cell line (10). In this study, the 46, X, i(Xq) karyotype was found in 23% of all patients, and half of them had mosaicism.

Mosaicism for a cell line with a normal or abnormal Y chromosome is identified in 6% to 11% of patients with TS with standard cytogenetic techniques. The identification of Y-chromosome material in females with TS is important due to the risk of gonadoblastoma. The prevalence of germ cell tumors is approximately 15% in 45, X/46, XY patients (11). The TS phenotype cannot predict the presence of a Y cell line. A phenotypic female may have no evidence of any androgen effect. Therefore, the patient will present as a phenotypic female with sexual infantilism and may have clitoromegaly. In the presence of an intra-abdominal streak and descended testes, frank ambiguity will be observed (10, 12). In this study, Y-chromosome abnormalities were detected in six (23%) patients, which is higher than that in current data. While one patient had isochromosome Y mosaicism, five patients had mosaicism with the 46, XY karyotype. Besides short stature, the most frequent feature was primary amenorrhea, which was found in four of the six patients, and none of them had genital ambiguity. Therefore, cytogenetic analysis should be performed earlier to lead to clinical management in patients with suspected Y-chromosome abnormalities.

Most patients with the 45, X/46, X, r(X) karyotype have a phenotype resembling the TS phenotype. However, patients with r(X) are at a higher risk of intellectual disability, learning difficulties, autistic spectrum disorders, and structural brain abnormalities due to the loss of the XIST region (13). In the current study, we found the 45, X/46, XX, r(X) karyotype in two patients. The developmental skills of these patients were normal, and none of them had intellectual disability. This may be related to the presence of the XIST locus and a functional gene in these two patients with the ring X chromosome. Further, intellectual disability was detected only in one patient who had the 45, X/47, XXX karyotype. She had cubitus valgus, a webbed neck, and short stature.

The most obvious features of TS are short stature, characteristic stigmata, and primary or secondary amenorrhea (2). In our study, short stature was found in 92.3% of the patients. Further, the characteristic TS stigmata with short stature were detected, particularly in patients with the 45, X karyotype. Therefore, these patients were diagnosed at earlier ages. The skeletal findings of our patients included short metacarpals and metatarsals. The cause of these features (short stature and other skeletal findings) in TS is thought to be due to a primary bone defect or due to the loss of the SHOX gene that is essential for growth (14).

Congenital cardiovascular disease is diagnosed in approximately half of the individuals with TS and is the major cause of mortality in adults. A bicuspid aortic valve is the most common congenital cardiac malformation, whereas coarctation of aorta accounts for approximately 10% of cardiac abnormalities in women with TS (14, 15). In our study, an echocardiographic examination was performed in 16 patients. Patent ductus arteriosus was detected in a patient in group 1, whereas mitral insufficiency was detected in two patients and left ventricular hypertrophy in one patient in group 2.

There is also an increased risk of celiac disease and developing ulcerative colitis in women with TS. X-chromosome abnormalities may play a role in the pathogenesis of inflammatory bowel disease. An increased susceptibility has been reported in women with the isochromosome Xq karyotype (16, 17). The incidence of autoimmune thyroid disease in females with TS increases with age. Previous studies have shown a doubling in the prevalence of autoimmune thyroid disease from the first to the third decade of life, being more prevalent in women with the isochromosome karyotype than in those with other karyotypes (9). In the present study, three patients had hypothyroidism, one of whom had a 46, X, i(Xq) karyotype. Furthermore, both hypothyroidism and celiac disease were detected in the two other patients with the mosaic karyotype.

Ear abnormalities and hearing loss are also common in TS, particularly in 45, X patients, and progressive sensorineural hearing loss is a major feature in adults (15). In our study, we detected hearing loss in two patients who had the 45, X karyotype. Both of them were 7 years old at the time of the diagnosis of hearing loss. Structural renal malformations, including horseshoe kidney and duplication of the collecting system, are found in up to 40% of patients with TS (16). While structural malformations of the kidney more frequently occur in pure 45, X patients, collecting system malformations more frequently occur in those with other TS karyotypes (17). In the present study, patients who had structural renal abnormalities (horseshoe kidney) had isochromosome and mosaic karyotypes, and this was inconsistent with the literature. Furthermore, abdominal ultrasonography revealed a simple cortical cyst in one of our patients with a mosaic karyotype.

Central nervous system malformations such as aberrant parietal cortex development, cerebellar vermis and pons hypoplasia, large fourth ventricle and cisterna magna, decreased parietal gray and occipital white matter, and increased cerebellar gray matter are seen in TS patients (18). In our study, corpus callosum agenesis was detected in a newborn with 45, X monosomy who had a webbed neck and edema of the hands and feet. This might be related to the haploinsufficiency of genes that escape X inactivation.

Study limitations

Our study had some limitations. It was a retrospective study with a small sample size and included limited long-term follow-up data.

CONCLUSION

Turner syndrome is a chromosomal disorder, and frequently, it is being misdiagnosed; therefore, any female with short stature and primary or secondary amenorrhea, with or without phenotypic features, should be evaluated with chromosome analysis. Mosaic karyotypes in TS are more frequent than previously thought; therefore, early recognition and diagnosis will improve the quality of life of such patients.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed consent: Written informed consent was obtained from patient.

Peer-review: Externally peer-reviewed.

Author's Contributions: Conceived and designed the experiments or case: ÖGB, DE, SG, ÖAK, EB. Performed the experiments or case: SG, ÖAK. Analyzed the data: EB, DE. Wrote the paper: SG, DE. All the authors have read and approved the final manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

- Nielson J, Wohlet M. Chromosome abnormalities found among 34910 newborn children: results from a 13 year incidence study in Arhus, Denmark. *Hum Genet* 1991; 87: 81-3. [\[CrossRef\]](#)
- Homer L, Le Martelot MT, Morel F, Amice V, Kerlan V, Collet M, et al. 45,X/46,XX mosaicism below 30% of aneuploidy: clinical implications in adult women from a reproductive medicine unit. *Eur J Endocrinol* 2010; 162: 617-23. [\[CrossRef\]](#)
- Hook EB, Warburton D. The distribution of chromosomal genotypes associated with Turner's syndrome: livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. *Hum Genet* 1983; 64: 24-7. [\[CrossRef\]](#)
- Held KR, Kerber S, Kaminsky E, Singh S, Goetz P, Seemanova E, et al. Mosaicism in 45,X Turner syndrome: does survival in early pregnancy depend on the presence of two sex chromosomes? *Hum Genet* 1992; 88(3): 288-94. [\[CrossRef\]](#)
- Davenport ML. Approach to the patient with Turner syndrome. *J Clin Endocrinol Metab* 2010; 95(4): 1487-95. [\[CrossRef\]](#)
- Oliveira RM, Verreschi IT, Lipay MV, Eça LP, Guedes AD, Bianco B, et al. Y chromosome in Turner syndrome: review of the literature. *Sao Paulo Med J* 2009; 127(6): 373-8. [\[CrossRef\]](#)
- McGowan-Jordan J, Simons A, Schmid M. *ISCN : an international system for human cytogenetic nomenclature*. Basel: New York, Karger; 2016. [\[CrossRef\]](#)
- Wolff DJ, Van Dyke DL, Powell CM. Laboratory guideline for Turner syndrome. *Genet Med* 2010; 12(1): 52-5. [\[CrossRef\]](#)
- Al Alwan I, Khadora M, Amir I, Nasrat G, Omair A, Brown L, et al. Turner Syndrome Genotype and phenotype and their effect on presenting features and timing of Diagnosis. *Int J Health Sci* 2014; 8(2): 195-202. [\[CrossRef\]](#)
- Zhong Q, Layman LC. Genetic considerations in the patient with Turner syndrome-45,X with or without mosaicism. *Fertil Steril* 2012; 98(4): 775-9. [\[CrossRef\]](#)
- Cools M, Drop SL, Wolffenbuttel KP, Oosterhuis JW, Looijenga LH. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. *Endocr Rev* 2006; 27: 468-84. [\[CrossRef\]](#)
- Gantt PA, Byrd JR, Greenblatt RB, McDonough PG. A clinical and cytogenetic study of fifteen patients with 45,X/46,XY Gonadal Dysgenesis. *Fertil Steril* 1980; 34: 216-21. [\[CrossRef\]](#)
- Kuntsi J, Skuse D, Elgar K, Morris E, Turner C. Ring-X chromosomes: Their cognitive and behavioural phenotype. *Ann Hum Genet* 2006; 64: 295-305. [\[CrossRef\]](#)
- Elsheikh M, Dunger DB, Conway GS, Wass JA. Turner's syndrome in adulthood. *Endocr Rev* 2002; 23(1): 120-40. [\[CrossRef\]](#)
- Bondy CA. Congenital cardiovascular disease in Turner syndrome. *Congenit Heart Dis* 2008; 3(1): 2-15. [\[CrossRef\]](#)
- Dhooge IJ, De Vel E, Verhoye C, Lemmerling M, Vinck B. Otologic disease in turner syndrome. *Otol Neurotol* 2005; 26(2): 145-50. [\[CrossRef\]](#)
- Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007; 92(1): 10-25. [\[CrossRef\]](#)
- Devernay M, Ecosse E, Coste J, Carel JC. Determinants of medical care for young women with Turner syndrome. *J Clin Endocrinol Metab* 2009; 94: 3408-13. [\[CrossRef\]](#)
- Sybert VP, McCauley E. Turner's Syndrome. *N Engl J Med* 2004; 351(12): 1227-38. [\[CrossRef\]](#)
- Chang P, Tsau YK, Tsai WY, Tsai WS, Hou JW, Hsiao PH, et al. Renal malformations in children with Turner's syndrome. *J Formos Med Assoc* 2000; 99(10): 796-8.
- Nijhuis-van der Sanden MWG, Eling PATM, Otten BJ. A review of neuropsychological and motor studies in Turner Syndrome. *Neurosci Biobehav Rev* 2000; 27: 329-38. [\[CrossRef\]](#)