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Original Article

The relationship between phenotypical findings and different karyotypes in children with turner syndrome

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Abstract

Aim: Turner syndrome (TS) is the most common chromosomal disorder in girls. Several systems can be adversely affected in association with genetic disorders. The purpose of this study was to examine the karyotype distribution in patients with TS, frequently seen clinical characteristics, and their relations with the karyotypes.

Materials and Methods: Fifty-four cases ranging in age between two and 40 years and diagnosed with TS at three different centers in Turkey between May 2013 and June 2019 were evaluated retrospectively.

Results: The patients' mean age was 17.5±9.3 years. The most common chromosomal anomaly was 45,X (35.2%), followed by low-level mosaic (20.4%), isochromosome (18.5%), deletion (9.3%) and other chromosomal disorders (16.7%). The most common presentation symptom was short stature (66.6%), followed by infertility (12.9%). Cardiovascular pathology was determined in 33.3% of cases, hypothyroidism in 25.9%, ophthalmological problems in 24.1%, renal anomaly in 18.5%, hearing loss in 12.9%, and scoliosis in 9.3% and mental retardation in 16.6%. Obesity was present in 33.3% of cases.

Conclusion: Turner Syndrome is a chromosomal disorder affecting several systems. Clinical manifestations in patients with TS can be affected to varying degrees depending on the karyotype.

Keywords: Children; karyotype; phenotype; turner syndrome

INTRODUCTION

Turner syndrome (TS) is the most common female chromosomal disorder seen in one in 1500-2500 live births, and resulting from partial or complete absence (monosomy) of the one X chromosomes (1). The most common karyotype is 45,X, followed by mosaic pattern, isochromosome X, ring X, and Xp and Xq deletions (2). Short stature and amenorrhea associated with primary gonadal failure are the main causes of presentation in TS. Other phenotypic features are short neck, low nuchal hairline, high palate, cubitus valgus, broad chest and widely spaced nipples, short 4th metacarpal bone, swelling in the hands and feet in the neonatal period and nail hypoplasia (3). Cardiac defects, renal malformations, thyroid disorders, sensorineural hearing loss, ophthalmological problems, gastrointestinal disorders, metabolic syndrome, dermatological pathologies, neurocognitive problems and neoplasias may also be seen in these cases (4). The phenotypic effect in TS cases depends on the type of chromosomal disorder (5). Phenotypic findings such as dysmorphic features, heart disease and kidney malformations have been associated with the degree of X chromosome loss. Studies have shown that the clinical features are more pronounced in Turner cases with 45,X karyotype. However, phenotypic findings may be milder in Turner cases with mosaic or isochromosome Xq karyotype (5). The purpose of this retrospective study was to analyze genetic variability in TS cases and its association with the phenotype.

MATERIALS and METHODS

Fifty-four cases ranging in age between two and 40 years and diagnosed with TS in three different regions of Turkey between May 2013 and June 2019 were included in the study. Data were retrieved from patients' medical records and age, reason for presentation, clinical and ultrasound examinations were evaluated retrospectively. Patients with a body mass index (BMI) greater than 95% were regarded as obese.

Genetic Analysis

Heparinized peripheral blood samples were collected, and cultured in incubators under conditions of 5% CO_2,

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37⁰C temperature and proper humidity. Slides including metaphase plates were obtained after cell culture. The slides were stained using the Trypsin and Giemsa (GTG) banding method, and examined under a microscope. Karyotype analysis was also performed. At least 20 metaphases were analyzed for each case. Results were evaluated based on the international system for human cytogenetic nomenclature (ISCN, 1981 and 1985) at 500–550 band resolution. All cases were also subjected to clinical, biochemical and radiological examination. The study was approved by the local ethics committee.

Statistical Analyses

All statistical analyses were performed on IBM SPSS® Statistics for Windows®, version 23.0 (IBM Corp., Armonk, NY, USA). The data were expressed as mean ± SD, median and range. Relations between Turner subgroups and other parameters were detected with the $\chi 2$ test. The Mann Whitney U test was used the comparison of two groups, and p values < 0.05 were considered statistically significant.

RESULTS

Fifty-four TS cases with different chromosomal compositions were included in the current study. The mean age of the cases was 17.5±9.3 years (min:2; max:44), and the mean height was 132.4±23.0 cm (min:77; max:172) (Table 1). In terms of chromosomal composition, 19 (35.2%) patients were 45,X, 11 (20.4%) were low mosaic, 10 (18.5%) were isochromosome, five (9.3%) were deletion, and nine (16.7%) represented other chromosomal composition types (Table 2). The most symptoms at presentation were short stature in 36 (66.6%) patients, abortus in three (5.5%), infertility in seven (12.9%) and delayed puberty in four (7.4%). Other presenting symptoms were obesity (3.7%), hypothyroidism (1.9%) and precocious puberty (1.9%).

Table 1. Chromosomal abnormalities of turner syndrome cases

Karyotype	n(%)
45,X	19(35)
45,X/46,XX	13(24)
46,X,i(X)(q10)/45,X	6(11)
46,X,i(X)(q10)	2(3.7)
46,X,del(X)(p21)	2(3.7)
45,X/47,XXX	2(3.7)
46,X,der(X),t(X,X)(p.11.2;q22)/45,X	1(1.8)
45,X/46,X,del(p.11.2)	1(1.8)
46,XX/46,X,del(X) (q26)/47,XXX	1(1.8)
46,X,der(x)/45,X	1(1.8)
45X/46X+mar	1(1.8)
45,X/46,X,i(X)(q10)/47,XX,i(X)(q10)	1(1.8)
45,X/46,X+mar/46,XX	1(1.8)
47,XX,+9/45,X	1(1.8)
46,X,der(X),del(X)(q22),dup(X)(p22.3p11.2)	1(1.8)
45,X,inv(9)(p12q13)/46,X,i(X)(q10),inv(9)(p12q13)	1(1.8)

Table 2. Characteristics of turner syndrome patients

Parameters	Mean(SD)
Age (years)	17.56 (9.31)
Height (cm)	132.46 (23.08)
SDS for height	-2.45 (1.43)
BMI (kg/m^2)	21.79 (5.21)
Weight (kg)	41.47 (20.04)
25-OH D (ng/mL)	21.95 (10.07)
Fasting Glucose (mg/dL)	96.86 (19.50)
Insulin (µIU/mL)	9.34 (4.59)
HbA1c (%)	5.60 (0.57)
ALT (U/L)	24.65 (18.41)
AST (U/L)	30.51(13.37)
LDL (mg/dL)	98.65 (25.60)
HDL (mg/dL)	49.07 (14.27)
Triglyceride (mg/dL)	101.10 (35.05)
Total cholesterol (mg/dL)	165.78 (26.75)
Hemoglobin (g/dL)	12.77 (1.71)
Vitamin B12 (pg/mL)	231.12 (65.95)
Folate (ng/mL)	8.48 (3.02)

BMI: Body mass index; SDS: Standard deviation score; LDL: low-density lipoprotein; HDL: High-density lipoprotein

Short stature was present in 17 (89.5%) of the patients with 45,X monosomy and in 19 (54.3%) patients with other karyotypes. The frequency of short stature was significantly higher in patients with 45, X karyotype than that of other karyotype groups (p=0.009). All patients with TS underwent transthoracic echocardiography for cardiac evaluation. Cardiovascular pathology was present in 18 (33.3%) of all TS patients, bicuspid aortic valve anomaly in six (11.1%), mild mitral insufficiency in four (7.4%) and mild tricuspid insufficiency in three (5.5%). Bicuspid aortic valve anomaly was present in five (26.3%) of the patients with the 45,X karyotype and other cardiovascular anomalies in four (21%). Bicuspid aortic valve anomaly was also present in one (2.8%) patient among the other non-45,X karyotypes and other cardiovascular anomalies in eight (22.8%). Hypertension was present in six patients (11.1%). All TS patients underwent renal ultrasonographic examination, and renal anomaly was observed in 10 (18.5%). Rates of renal anomaly were 36.8% in patients with the 45,X karyotype and 8.6% in cases with other karyotypes. Hypothyroidism was present in 14 (25.9%) patients. Six (31.5%) of the cases with the 45,X karyotype and eight (22.9%) of those with other karyotypes were diagnosed with hypothyroidism. Anti-TPO positivity was determined in nine (16.6%) patients and anti-TG positivity in 10 (18.5%). No difference was observed between the karyotypes in terms of prevalences of autoantibody positivity and hypothyroidism. Hearing loss was present in seven (12.9%) patients and ophthalmological problems in 13 (24.1%).

Table 3. Distribution of common pathologies according to karyotypes in turner syndrome patients

Parameters	45,X n(%)	Others n(%)	χ2	p
Short stature	17(89.5)	19(54.3)	6.862	**0.009***
Obesity	2(10.5)	16(45.7)	6.862	**0.009***
Cardiovascular anomalies	8(42.2)	10(28.6)	1.015	0.314
Renal anomalies	7(36.8)	3(8.6)	6.523	**0.011***
Hypertension	1(5.3)	5(14.3)	1.015	0.314
Hypothyroidism	6(31.6)	8(22.9)	0.488	0.485
Anti-TPO	3(15.8)	6(17.1)	0.016	0.899
Anti-TG	4(21.1)	6(17.1)	0.125	0.724
Mental retardation	3(15.8)	6(17.1)	0.016	0.899
Hearing problems	2(10.5)	5(14.2)	0.154	0.694
Eye problems	4(21)	9(25.7)	0.146	0.702
Scoliosis	3(15.8)	2(5.7)	1.488	0.332
Short neck	11(57.9)	17(48.6)	0.429	0.513

Anti-TPO: Anti–thyroid peroxidase; Anti-TG: Antithyroglobulin

Table 4. Comparison of patients with 45,x and other karyotypes in turner syndrome

	45,X(n=19)		Others(n=35)			
Parameters	Mean±SD	Median(range)	Mean±SD	Median(range)	Z	p
Age (years)	14.026±7.056	11.5 (21.45)	19.486±9.897	14.5 (30.79)	-2.087	**0.037***
Height (cm)	123.511±20.919	122.75 (20.95)	137.326±23.014	144 (31.06)	-2.255	**0.024***
SDS for height	-2.778±1.028	-3.365 (23.26)	-2.275±1.605	-2.450 (29.09)	-1.317	0.188
BMI (kg/m^2)	19.567±4.219	16.90 (21.08)	23.003±5.361	22.71 (30.99)	-2.210	**0.027***
Weight (kg)	31.929±15.595	27 (20.32)	46.657±20.472	52.5 (31.4)	-2.473	**0.013***
25-OH D (ng/mL)	21.855±10.990	28.5 (26.05)	22.004±9.685	20.835 (26.76)	-0.162	0.872
Fasting Glucose (mg/dL)	95.516±10.446	94.5 (26.89)	98.134±23.033	96 (27.83)	-0.208	0.835
Insulin (µIU/mL)	9.337±5.057	7.95 (26.26)	9.349±4.387	7.7 (27.41)	-0.260	0.795
HbA1c (%)	5.590±0.290	5.65 (26.82)	5.606±0.692	5.80 (27.1)	-0.065	0.948
ALT (U/L)	26.619±25.742	22 (25.06)	23.699±13.973	23.5 (24.97)	-0.021	0.983
AST (U/L)	36.519±18.669	28.50 (28.81)	27.602±8.832	28 (23.15)	-1.301	0.193
LDL (mg/dL)	91.846±29.008	107 (17.73)	102.054±23.593	111 (21.13)	-0.897	0.379
HDL (mg/dL)	51.462±16.287	42 (21.15)	47.874±13.339	41 (19.42)	-0.447	0.655
Triglyceride (mg/dL)	92±28.554	90 (17.12)	105.653±37.576	100 (21.44)	-1.118	0.264
Total cholesterol (mg/dL)	157.385±23.929	166 (15.73)	170.156±27.551	174 (21.46)	-1.508	0.132
Hemoglobin (g/dL)	13.048±1.387	12.9 (27.85)	12.625±1.863	12.85 (23.48)	-1.019	0.308
Vitamin B12 (pg/mL)	233.618±48.970	236.5 (20.18)	230.069±75.413	203.5 (18.50)	-0.432	0.666
Folate (ng/mL)	8.716±2.508	8.55 (16.67)	8.376±3.280	7.255 (14.25)	-0.707	0.479

BMI: Body mass index; SDS: Standard deviation score; LDL: low-density lipoprotein; HDL: High-density lipoprotein

Orthopedist evaluation revealed scoliosis in five (9.3%) cases, and mental retardation was determined in 16.6% of cases at psychiatric assessment. Obesity was present in 33.3% of cases. Obesity was more common in patients with other karyotype groups (45.7%), and its frequency was significantly higher than that of 45,X karyotype (10.5%) (p=0.009) (Table 3). When the patients divided two groups as patients with 45,X and other karyotypes, statistically significant differences were found between the groups for age (p=0.037), height (p=0.024), BMI (p=0.027) and weight (p=0.013) (Table 4) .

DISCUSSION

The most common chromosomal disorder in TS patients is 45,X monosomy, followed by the mosaicism form (2). Studies have identified 45,X/46,XX and 45,X/46,X,i(Xq) as the most frequently seen mosaic forms, and isochromosome Xq is the most commonly reported X

chromosome abnormality (3). Consistent with the previous literature, 45,X monosomy was detected in 35.2% of our cases, low-level mosaicism in 20.4%, isochromosome X in 18.5%, deletion in 9.3% and other types of chromosomal disorder in 16.7%.

Turner Syndrome is generally diagnosed late. Yeşilkaya et al. reported a mean age at diagnosis of 10.2±4.4 years (4). The mean age at diagnosis in the present study was 17.5±9.3 years. We attributed our higher mean age at diagnosis to that reported by Yeşilkaya et al. to adult women being included in addition to children and adolescents in this study.

Loss of the short stature–homeobox (SHOX) gene located on the pseudoautosomal region of the short arm of the X chromosome is thought to lead to short stature, which is the most common presentation symptom among TS patients (4). If these cases are not treated, they are approximately 20-21 cm shorter than normal adults in their own communities (6). Studies have reported short stature rates at the first presentation between 51.1% and 70% in TS patients (4,7). The rate of TS patients presenting with short stature in the present study was 66.6%, a figure consistent with the previous literature. The severity of shortness of stature in TS patients is reported to vary depending on the karyotype. Al Alwan et al. reported short stature in all cases (100%) of 45,X monosomy and in 77.8% of patients with other karyotypes (5). Similarly, the prevalence of short stature in the present study was higher in cases with the 45,X karyotype (89.5%) than in those with other karyotypes (54.3%).

Spontaneous pubertal development is generally absent due to ovarian dysgenesis in the majority of women with TS, and these patients are generally infertile (8). In addition, spontaneous puberty develops in 25-30% of cases. The rate of spontaneous pubertal development is higher in girls with the mosaic karyotype. Spontaneous menarche is rare in TS cases, and this is followed by premature menopause. Natural pregnancy occurs in only 2% of women. Some patients with TS may be identified in adulthood when being investigated for the cause of secondary amenorrhea or infertility (9). Similarly, seven (12.9%) of our cases aged over 18 were diagnosed with TS during infertility investigation and three (5.5%) during abortus investigation. Delayed puberty was also the reason for presentation in four (7.4%) of our cases.

Cardiovascular system anomalies are the most important life-threatening problem in TS patients. Such anomalies are reported in 50% of adults with TS, although this ranges between 25% and 30% in pediatric cases (4,10,11). The cardiovascular system anomaly rate in the present study was 33.3%, a figure consistent with previous research. The most common congenital heart problem in TS patients is a bicuspid aortic valve. Other cardiological problems include aortic coarctation, atrial and ventricular septal defects and partial abnormal pulmonary venous connection (12,13). Consistent with previous studies, the bicuspid aortic valve rate in the present research was 11.1%. Studies have reported a higher incidence of cardiac anomaly in patients with the 45,X chromosome than in those with other chromosomal structures (12,13). The incidence of cardiac anomaly in the present study was higher in cases with 45,X monosomy (42.2%) compared to in cases with other karyotypes (28.6%). Similarly, the incidence of bicuspid aortic valve anomaly was also higher in cases with 45,X monosomy (26.3%) compared to those with other karyotypes.

Hypertension is seen in 13-58% of adults with TS and in one in four children (14). Hypertension in TS is thought to be multifactorial. Obesity, metabolic syndrome, abnormal vasculature, renal anomalies, dyslipidemia and estrogen deficiency constitute risk factors for the development of hypertension (15). The effect on the pathogenesis of hypertension of the renin-angiotensin-aldosterone system is uncertain. An association between increased plasma renin activity and arterial hypertension was determined in young women with TS (16), although this was not confirmed in another study (17). The incidence of hypertension in the present study was 11.1%, lower than that in previous research. This may be due to blood pressure measurement being overlooked in some subjects or measurement technique errors.

Structural kidney malformations are seen in approximately 40% of TS patients (18). The most common such anomalies are horseshoe kidney and duplex collecting system anomalies. The prevalence of renal pathology in the present study was 18.5%, and consistent with the literature, this was higher in cases with the 45,X chromosome than in those with other chromosomal anomalies.

The risk of Hashimoto's thyroiditis and associated thyroid function disorder increases in girls with TS. Thyroid antibody positivity ranged between 10.4% and 45%, and the prevalence of hypothyroidism ranges between 11.1% and 33% (4,19). Consistent with the previous literature, the prevalence of anti-TPO was 16.6% in the present study, that of anti-TG positivity 18.5%, and that of hypothyroidism 25.9%. Autoimmune thyroid diseases are also reported to be more common in cases with isochromosome karyotype than in cases with other karyotypes (4). However, no difference was determined between karyotypes in terms of prevalences of autoantibody positivity and hypothyroidism in the present study.

Hearing loss may be seen in 20-30% of TS cases (20-22). Hearing loss is usually conductive type at early ages, while sensorineural type loss develops at later ages. Hearing loss has rarely been reported in mosaic TS cases (3). A lower prevalence of hearing loss (12.9%) was determined in this study compared to the previous literature. This suggested that the non-hearing loss case group should be re-evaluated for hearing loss. Ophthalmological problems may also be seen in TS patients. Wikiera et al. reported that vision impairment was most commonly determined in TS patients, followed by strabismus, changes in the posterior segment, red-green color deficiency and changes in the

anterior segment, but that no correlation was determined between karyotype and ocular disorders (23). We identified ophthalmological problems in 24.1% of cases in this study, and in agreement with the literature, we found no relation between ocular defects and karyotype.

The risk of scoliosis development is higher in girls with TS than in normal individuals, and the incidence increases with age. The prevalence of scoliosis in individuals with TS in previous studies ranges between 10% and 20% (1). Scoliosis was observed in 9.3% of cases in the present study. Since the risk of scoliosis is reported to increase as stature increases in girls with TS, cases receiving growth hormone therapy must be closely monitored in terms of scoliosis development (24).

Emotional problems and learning difficulties may also be seen in patients with TS (25). With the exception of cases with a marker chromosome or ring (X) chromosome, intelligence is generally normal. Van Dyke et al. reported mental retardation in 6.9% of TS patients (26). Mental retardation in that study of 174 cases was determined in one of the cases with a 45,X chromosome (1/70), but in all small r(X) cases (6/6). Mental retardation was present in 16.6% of the TS cases in the present study. Additionally, and consistent with the previous literature, the prevalence of mental retardation was higher in other karyotypes cases than in those with 45,X.

Obesity may be seen in girls with TS due to low physical activity and a sedentary life style. Glucose metabolism disorders such as insulin resistance and impaired glucose tolerance emerging in these cases have been linked to obesity. It is therefore important to inculcate habits such as physical activity and healthy nutrition from an early age in cases with TS. The prevalence of obesity in TS patients in previous studies ranges between 9.5% and 24.7% (4,27). Obesity was present in 33.3% of our cases. The higher rate of obesity in this study compared to the literature was attributed to the sociocultural structure of and the nutritional habits in our region.

CONCLUSION

In conclusion, TS is a complex entity affecting several systems. In addition, the severity of clinical findings in TS patients may vary depending on the relationship between karyotype and phenotype. Diagnosis may be delayed until adulthood in cases with mild clinical findings. These cases must be followed-up and treated with a multidisciplinary team approach.

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