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RESEARCH

Cardiovascular Manifestations of Turner Syndrome: Phenotypic Differences Between Karyotype Subtypes

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Abstract

Turner syndrome (TS) is a genetic disorder presenting in phenotypic females with total or partial monosomy of the X chromosome. Cardiovascular abnormalities are common, including congenital heart defects (CHD) and aortic dilation. Although mosaic TS is suspected to have less severe phenotype as compared to non-mosaic TS, differences in cardiovascular manifestations between karyotypes are not well studied. This is a single-center retrospective cohort study including patients with TS seen from 2000 to 2022. Demographic data, chromosomal analysis, and imaging were reviewed. Karyotypes were categorized as monosomy X (45X), 45X mosaicism, isochromosome Xq, partial X deletions, ring X (r(X)), TS with Y material, and others. Prevalence of CHD and aortic dilation were compared between monosomy X and other subtypes using Pearson's chi-square test and Welch two-sample t-test. We included 182 TS patients with median age 18 (range 4–33) years. CHD was more common in monosomy X as compared with others (61.4% vs. 26.8%, $p<0.001$), including bicuspid aortic valve (44.3% vs. 16.1%, $p<0.001$), partial anomalous pulmonary venous return (12.9% vs. 2.7%, $p=0.023$), persistent left superior vena cava (12.9% vs. 1.8%, $p=0.008$), and coarctation of the aorta (20.0% vs. 4.5%, $p=0.003$). Cardiac surgery (24.3% vs. 8.9%, $p=0.017$) was more prevalent in the monosomy X group. There was no statistically significant difference for presence of aortic dilation (7.1% vs 1.8%, $p=0.187$). Although CHD and need for cardiac surgery are more common in TS with monosomy X as compared to others, all TS subtypes may have similar risk of developing aortic dilation. All TS patients should have similar cardiovascular surveillance testing to monitor for aortic dilation.

Keywords Turner syndrome · Congenital heart disease · Bicuspid aortic valve · Coarctation of the aorta · Aortic dilation

Introduction

Turner syndrome (TS) is one of the most common genetic disorders, affecting 1 in 2000 female live births, and is characterized by complete or partial monosomy X [1, 2]. Karyotype variations in TS can be divided in two main groups: aneuploidy and structural abnormalities of the X chromosome. Additionally, the X chromosome abnormalities can exist in mosaic forms where only some cells of the body are affected. Cardiac manifestations in TS include congenital cardiac disease (CHD), the most common being bicuspid aortic valve, coarctation of the aorta, persistent left superior vena cava, and partial anomalous pulmonary venous return [1–4]. These individuals are also at increased risk of developing aortic dilation and possibly dissection [5]. There are multiple consensus statements describing the care of patients with TS [1, 6, 7], including guidelines from the American Heart Association for screening and management

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of TS patients for presence of congenital heart defects and monitoring for aortic dilation and dissection. The frequency of cardiac imaging recommended by these guidelines is dependent on the presence or absence of congenital disease, and on the presence of aortic dilation as measured via Turner-specific z-scores for patients < 15 years of age and aortic size index (ASI) for patients > 15 years of age [7, 8]. Currently, there is no differentiation in the management guidelines based on karyotype [7, 8].

Several studies have evaluated the relationship between karyotype and cardiovascular manifestations in TS, with conflicting results. A large study of 611 TS patients reported evaluating overall comorbidities including hearing, cardiovascular, endocrine, autoimmune, and bone health abnormalities, with lower prevalence of associated comorbidities and phenotypic features of disease in partial monosomy X or mosaic TS as compared to individuals with complete monosomy X [9]. This study reported lower prevalence of bicuspid aortic valve in mosaic TS. However, other CHD lesions were not compared. Similarly, significant differences between the rates of bicuspid aortic valve and aortic dilation have been reported between patients with complete monosomy X and mosaic variants [10, 11]. However, other studies have not noted significant difference in cardiac manifestations between karyotypes [12, 13]. Better understanding of the correlation between karyotype and phenotype will improve clinician ability to appropriately counsel patients on CHD risk and acquired heart disease. The goal of this study is two-fold: (1) to evaluate the prevalence of CHD and aortic dilation in TS with different karyotype subtypes and (2) to compare the prevalence of each manifestation between complete monosomy X and mosaic TS.

Methods

Study Design

The institutional review board at Ann & Robert H Lurie Children's Hospital of Chicago approved this retrospective cohort study (IRB-2022–5214).

Study Population

We included all patients with TS diagnosis seen at Ann & Robert H. Lurie Children's Hospital of Chicago from 2000 to 2022. Inclusion criteria included those who had chromosome analysis results available for our review to confirm the karyotype, and diagnosis of partial or complete monosomy of the X chromosomes. Patients with male phenotype, non-binary genitalia, and mixed gonadal dysgenesis (MGD) were excluded.

Data sources consisted of the electronic medical record, genetic test results, echocardiography database and MRI database. Data were collected for each patient via their clinic notes, laboratory test results, echocardiogram reports, and MRI reports. Karyotypes were reviewed and the cohort was divided into 7 subtypes, including monosomy 45,X, 45,X mosaicism (e.g., 45,X/46,XX and 45,X/46,XX/47,XXX and variants), isochromosome Xq, partial X chromosome deletions considered TS per guidelines [14], ring X chromosome (r(X)), Turner syndrome with Y material (e.g., 45,X/46,XY and 45,X/46,X,idicYq11.2 and variants), and other.

Cardiac Imaging Data

CHD types and prevalence were determined based on review of latest echocardiogram and MRI reports. Number of cardiac diagnoses was determined from the number present of coarctation, bicuspid aortic valve, partial anomalous pulmonary venous return, persistent left superior vena cava, and other. Cardiac diagnoses in the other category include VSD, ASD, PDA, dilated cardiomyopathy, mild coronary anomalies (high RCA takeoff, coronary artery fistula, coronary artery to PA fistula), aberrant right subclavian artery, Scimitar syndrome, dilated cardiomyopathy, hypoplastic left heart, and double outlet right ventricle with malposed great arteries. Presence of aortic dilation was based on the latest echocardiogram or MRI for patients without a history of cardiac surgery involving the aortic arch. For those with history of arch reconstruction, the last echocardiogram and/or MRI reports prior to cardiac surgery were reviewed. Aortic root and ascending aorta measurements were collected from imaging reports, and TS specific z-scores for these were calculated as described by Quezada, et al.[8] For patients older than 15 years of age, aortic size index (ASI), which represents the ratio of the aortic diameter to body surface area, was also calculated. Aortic dilation was defined as having either a TS specific Z-score > 2 in patients under 15 years or ASI > 2 cm/m^2 in patients greater than 15 years of age.

Statistical Analysis

Statistical analysis was carried out using Stata [15, 16]. Discrete variables were summarized as counts and percentages, while continuous variables were presented as median with interquartile range and percentages. The study cohort was divided based on karyotype into seven groups, as described above. Cardiac disease prevalence in the form of CHD and aortic dilation was compared between the complete monosomy 45, X group versus the six other TS karyotype subtypes collectively. Bivariate analyses were performed for comparison of candidate factors between these two groups using the Wilcoxon rank sum test, Chi-squared test, and Welch two-sample *t*test.

Results

Baseline Population Characteristics

We collected data on 182 patients with TS that met inclusion criteria. Patient demographics and karyotypes are described in Table 1. There was no statistically significant difference regarding age, race or ethnicity of patients with different karyotypes. The karyotype distribution in our study cohort is like those reported in prior studies, as seen in Table 1 [9, 17, 18]. There was one patient death in our cohort.

Association Between Karyotype and Phenotype

The prevalence and forms of CHD seen in different subtypes of TS based on karyotype are described in Table 2. The prevalence of all types of CHD, as well as individual types of cardiac disease, including bicuspid aortic valve, coarctation of the aorta, persistent left superior vena cava, and partial anomalous pulmonary venous return was higher in patients with 45,X karyotype as compared to patients with other karyotypes. In addition, individuals with 45,X karyotype were more likely to have more than one CHD per patient and more likely to have needed cardiac surgical interventions for the CHD as compared to those with other karyotypes. The most common surgery needed by this patient population was coarctation repair, followed by surgical repair of aortic dilation, aortic valvuloplasty, partial anomalous pulmonary venous return repair, single ventricle palliation, and closure of ventricular septal defect. In contrast, there was no statistically significant difference in development of aortic root dilation or ascending aortic dilation between those with 45, X karyotype and others based on their echocardiogram and MRI findings (Table 3).

Discussion

This study describes prevalence and types of CHD, need for cardiac surgery, and development of aortic dilation in different karyotype subtypes of Turner syndrome. Although TS individuals with mosaicism and partial monosomy X have lower risk of CHD as compared to those with complete monosomy 45,X, the risk of aortic dilation is not statistically different between the groups.

Prevalence of Congenital Heart Disease in TS Subtypes

Our data suggest that individuals with the non-mosaic 45,X karyotype of TS have higher prevalence of CHD and higher rates of need for cardiac surgical intervention as compared to TS individuals with other karyotypes. In our overall cohort, 40% of TS patients had CHD, similar to previously reported ranges [19].

However, prior data related to specific CHD prevalence in different karyotype subtypes are limited or conflicting. In one study of 202 individuals with TS, 35% of whom were of complete 45,X karyotype, the authors did not find significant difference in rates of BAV or coarctation between the 45,X karyotype and all other subtypes [12]. In another study of 101 individuals with TS, of which 45% were of the 45,X karyotype, the prevalence of BAV (32% in 45,X vs. 17% in others) and coarctation (16% in 45,X vs. 6% in others) was

Table 1 Demographic characteristics, overall and by grouping

Turner syndrome groupings								
	Overall *N* = 182	Group 1 45X *N* = 70 (39%)	Group 2 mosaic 45X/46XX *N* = 48 (26%)	Group 3 isochromosome Xq *N* = 32 (18%)	Group 4 X deletion *N* = 8 (4%)	Group 5 r(X) *N* = 9 (5%)	Group 6 TS with Y material *N* = 13 (7%)	Group 7 other *N* = 2 (1%)
Race/ethnicity, N(%)								
White	83 (45.6)	31 (44.3)	23 (47.9)	18 (56.3)	–	2 (22.2)	4 (30.8)	–
Hispanic or Latino	69 (37.9)	1 (1.4)	17 (35.4)	8 (25.0)	1 (12.5)	4 (44.4)	6 (46.2)	1 (50.0)
Asian	10 (5.5)	2 (2.9)	2 (4.2)	3 (9.4)	–	1 (1.1)	1 (7.7)	1 (50.0)
African American	6 (3.3)	1 (1.4)	2 (4.2)	1 (3.1)	–	1 (1.1)	1 (7.7)	–
Other	8 (4.4)	2 (2.9)	2 (4.2)	2 (6.2)	–	1 (1.1)	1 (7.7)	–
Age, years								
Median (IQR)	18 (13, 23)	19 (12, 23)	17 (14, 20)	21 (16, 25)	19 (14, 27)	18 (16, 19)	18 (13, 26)	10 (8, 13)

– is 0 (0)

Table 2 Congenital heart disease in patients with Turner syndrome

Turner syndrome groupings										
	Overall *N* = 182	Group 1 45X *N* = 70 (39%)	All Other Groups *N* = 112 (61%)	p-value	Group 2 mosaic 45X/46XX *N* = 48 (26%)	Group 3 isochromosome Xq *N* = 32 (18%)	Group 4 X deletion *N* = 8 (4%)	Group 5 r(X) *N* = 9 (5%)	Group 6 TS with Y material *N* = 13 (7%)	Group 7 other *N* = 2 (1%)
Congenital heart disease	73 (40.1)	43 (61.4)	30 (26.8)	< 0.001	16 (33.3)	4 (12.5)	1 (12.5)	4 (44.4)	4 (40.8)	1 (50.0)
Number of CHD diagnoses										
One	45 (24.7)	22 (31.4)	23 (20.5)	0.001	12 (25.0)	3 (9.4)	1 (12.5)	3 (33.3)	3 (23.1)	1 (50.0)
Two	19 (10.4)	11 (15.7)	8 (7.1)		4 (8.3)	2 (6.3)	–	1 (11.1)	1 (7.7)	–
Three	7 (3.9)	6 (8.6)	1 (0.9)		1 (2.1)	–	–	–	–	–
Four	2 (1.1)	2 (2.9)	–		–	–	–	–	–	–
Type of CHD										
BAV	49 (26.9)	31 (44.3)	18 (16.1)	< 0.001	9 (18.8)	3 (9.4)	–	3 (33.3)	3 (23.1)	–
Coarctation	19 (10.4)	14 (20.0)	5 (4.5)	0.003	4 (8.3)	–	–	–	1 (7.7)	–
Coarctation and BAV	16 (8.8)	11 (15.7)	5 (4.5)	0.009	4 (8.3)	–	–	–	1 (7.7)	–
PAPVR	12 (6.7)	9 (12.9)	3 (2.7)	0.023	1 (2.1)	2 (6.3)	–	–	–	–
LSVC	11 (6.0)	9 (12.9)	2 (1.8)	0.008	0 (0)	1 (3.1)	–	1 (11.1)	–	–
Other	21 (11.5)	7 (10.0)	14 (12.5)		9 (18.8)	1 (3.1)	1 (12.5)	1 (11.1)	1 (7.7)	1 (50.0)
Cardiac surgical history	26 (14.3)	17 (24.3)	9 (8.0)	0.009	6 (12.5)	2 (6.3)	–	–	1 (7.7)	–
Coarctation repair	15 (8.2)	11 (15.7)	4 (3.6)		3 (6.3)	–	–	–	1 (7.7)	–
Aortic repair	4 (2.2)	3 (4.3)	1 (0.9)		–	1 (3.1)	–	–	–	–
Both	2 (1.1)	2 (2.9)	–		–	–	–	–	–	–
Other	5 (2.8)	1 (1.4)	4 (3.6)		3 (6.3)	1 (3.1)	–	–	–	–

LSVC Persistent left superior vena cava, *PAPVR* partial anomalous pulmonary venous return, *BAV* bicuspid aortic valve, *CoA* coarctation of the aorta,—is 0 (0), Aortic repair includes arch augmentation, replacement of any of aortic root, ascending or transverse arch, and Bentall procedure

Table 3 Aortic root and ascending aorta dilation in patients with Turner syndrome

Turner syndrome groupings										
	Overall *N* = 182	Group 1 45X *N* = 70 (39%)	All Other Groups *N* = 112 (61%)	*p*-value	Group 2 mosaic 45X/46XX *N* = 48 (26%)	Group 3 isochromosome Xq *N* = 32 (18%)	Group 4 X deletion *N* = 8 (4%)	Group 5 r(X) *N* = 9 (5%)	Group 6 TS with Y material *N* = 13 (7%)	Group 7 Other *N* = 2 (1%)
Aortic root dilation										
Seen by ECHO	2 (1.1)	1 (1.4)	1 (0.9)	0.913	1 (2.1)	–	–	–	–	–
Seen by MRI	7 (3.9)	5 (7.1)	2 (1.8)	0.176	1 (2.1)	1 (3.1)	–	–	–	–
By ECHO or MRI	7 (3.9)	5 (7.1)	2 (1.8)	0.187	1 (2.1)	1 (3.1)	–	–	–	–
Ascending aorta dilation										
Seen by ECHO	6 (3.3)	4 (5.7)	2 (1.8)	0.35	–	2 (6.3)	–	–	–	–
Seen by MRI	4 (2.2)	3 (4.3)	1 (0.9)	0.277	–	1 (3.1)	–	–	–	–
By ECHO or MRI	7 (3.9)	5 (7.1)	2 (1.8)	0.188	–	2 (6.3)	–	–	–	–

– is 0 (0)

not found to be statistically significant between the complete 45,X and other karyotypes [13]. In a different study of 105 individuals with TS (45% with 45,X karyotype), the presence of BAV (15% in 45,X vs. 0% in others) was found to be statistically significant between the groups, but coarctation (3% in 45,X vs. 0% in others) was not. However, this comparison may be limited by the overall low number of anomalies present in patients in this study [10]. Separately, a study of 118 individuals with TS revealed that those with > 70% 45,X cells on karyotype analysis (including complete monosomy 45,X) were more likely to present with BAV than those with < 70% 45,X cells, indicating a possible dose dependence of 45,X [11]. Of note, there is lack of uniformity in how karyotypes are compared in the literature (i.e., 45, X vs. the rest or 45,X vs. individual types of karyotypes), which may also contribute to some of the variation in reported results.

Based on our findings, we continue to suggest screening of all individuals with TS for congenital heart disease at the time of diagnosis, either prenatally or after birth. However, with prenatal genetic diagnosis of or suspicion for TS in the unborn child, the expectant parents should be counseled regarding risk of CHD associated with TS based on the fetal karyotype. This counseling should include an explanation of the lower risk of CHD in mosaic and partial monosomy X as compared to complete or non-mosaic TS. Our study findings strengthen the prior reports that monosomy X karyotype has higher risk of having CHD and need for cardiac surgical interventions early in life. This information provides an opportunity for more individualized counseling based on karyotype.

Acquired Aortic Dilation

Patients with monosomy 45,X have been shown to have a higher mortality rate than other TS karyotypes, with aortic dissection as a main contributor to mortality [20, 21]. In our data, the differences in prevalence of aortic root or ascending aorta dilation between individuals with 45,X and other karyotypes did not reach statistical significance. At least one other study also found similar rates of aortic dilation between different TS genotypes, with rates of 13% in the 45,X group vs. 17% in all others, with a total study size of a 101 patients, all age 18 or under, with median age 10 years [13]. A similarly sized study of 105 patients demonstrated a statistically significant difference between the presence of aortic dilation in those with 45,X karyotype (32.5%) and all others (6.2%), though this cohort was slightly older than ours with mean age 24 years, and mean age at dilation diagnosis of 25.6 years [10]. Aortic dilation has also been found to be dose dependent on karyotype in one study, with those exhibiting < 70% 45,X cell on karyotype being less likely to have aortic dilation with an OR of 0.19 [11].

Our cohort is drawn from a pediatric and young adult Turner syndrome center with median age of 18 years, which likely underestimates lifelong prevalence of aortic dilation as this is a more common finding in adults with TS [22]. The number of patients with these pathologies was therefore low in our cohort and inference is limited to patients with similar demographics, i.e., younger/pediatric patients. In our younger TS patients, karyotype did not reach statistically significant impact on the presence or absence of acquired aortic pathology. As such, it would be reasonable to continue screening patients of all TS karyotypes for aortic pathology at similar intervals at younger ages. Given that aortic pathology often develops after childhood, it is possible that this recommendation would be different if an older patient population had been studied.

Findings for Individual Genotypes

Multiple studies have been published comparing the mosaic monosomy X TS group to the non-mosaic 45,X group, with the suggestion that mosaicism leads to less severe phenotype in a dose dependent manner [11]. This was the second most common karyotype seen in our study population, and while the CHD prevalence of 33% is higher than for the normal population, it is less than in the non-mosaic 45,X group. Previously it was reported that while other parts of the TS phenotype are similar to those with non-mosaic 45,X, patients with isochromosome Xq do display a less severe cardiac phenotype [9, 17]. Our data are consistent with this finding, with isochromosome patients appearing to have lower prevalence of CHD as compared to the non-mosaic 45,X TS subgroup. The group of patients with X chromosome deletion leading to TS is not well described in the literature and was one of the smallest in this study, consisting of 8 patients and there was only one patient in this group in this study with congenital heart disease. Thus, sample size is a significant limitation for this subgroup and further research is needed on a larger cohort of individuals with TS and X chromosome deletions. Previous studies suggest that patients with ring chromosome have lower CHD risk than those with 45,X [9, 17]. In our study, this group of patients was too small for inference testing to return meaningful results, but the rate of CHD in this group appeared similar to that of the 45,X group, mostly as bicuspid aortic valve. Other studies have found patients with TS with Y material karyotype variation to have similar levels of cardiac disease to the monosomy 45,X group [9, 17]. This subgroup was very small in our study, so inference testing could not be performed on this subsample, though the rate of congenital heart disease in this group was similar to that of the 45,X group, mostly with bicuspid aortic valve.

Limitations

Our study suggests that there are phenotypic differences in pediatric TS patients based on their karyotype, particularly when comparing patients with complete monosomy 45,X to all other karyotype variations collectively. While this is a sizable pediatric cohort, there were not enough patients to perform more specific phenotype to karyotype comparisons. A larger, multi-institutional study of these patients would be beneficial for understanding the rarer karyotypes. This was a retrospective study performed on patients seen in a pediatric center, with median age 18 years, which is younger than the age at which aortic pathology is generally found in TS. A study focusing on either a large adult cohort or prospectively following a pediatric cohort into adulthood would aid in understanding the relationship between karyotype and aortic dilation.

Conclusion

TS patients with 45,X karyotype are at greater risk of CHD and need for pediatric cardiac surgery as compared to those with other karyotype variations. However, the risk of aortic dilation may be similar between the two groups. This information will help guide prenatal counseling on cardiac risk based on karyotype. We suggest that congenital and acquired heart disease screening should remain similar for patients of all TS karyotypes until more data is available.

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Declarations

Competing Interests The authors have no competing interests to declare that are relevant to the content of this article.

Ethical Approval The institutional review board at Ann & Robert H Lurie Children's Hospital of Chicago approved this retrospective cohort study (IRB-2022–5214).

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