HEART AND AORTA ANOMALIES IN TURNER SYNDROME AND RELATION WITH KARYOTYPE

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Abstract

Objectives. Turner Syndrome (TS) is associated with a high risk of cardiac anomalies and cardiovascular disease. We aimed to evaluate patients with TS (n=33) for cardiac and aortic pathology using thorax magnetic resonance angiography (MRA).

Subjects and methods. Clinical findings, karyotypes, echocardiogram (ECHO) findings and thorax MRA results were evaluated. Aortic dimensions were measured and standard Z scores of aortic diameters along with aortic size index (ASI) were calculated.

Results. Mean age of the patients was 13.7±3.4 years. MRA revealed cardiovascular pathology in 10 patients (30%). CoA (n=4), aberrant right subclavian artery (n=3), dilatation of the ascending aorta (n=1), tortuosity of the descending aorta (n=1) and fusiform dilatation of the left subclavian artery (n=1) were found. Two of the four patients with CoA found on MRA were detected with ECHO. Mean diameter of the sinotubular junction was found to be elevated [mean±SD: 2.4±1.5]. Z scores for the diameters of the isthmus, ascending aorta and descending aorta were in normal ranges. 45,X patients were found to have significantly higher ASI values than non 45,X patients (p=0.036).

Conclusion. Our findings indicate that patients with TS should be evaluated with MR imaging studies in addition to ECHO to reveal additional subtle cardiac and vascular anomalies. CoA which is very distally located or which has mild nature may not be seen by ECHO. The increase in ASI observed in 45,X patients may herald the development of life-threatening complications. Therefore, frequent follow-up is warranted in these patients.

Keywords: aortic dilatation, cardiovascular, thorax angiography, Turner syndrome.

INTRODUCTION

Turner syndrome (TS) is a chromosomal disorder of phenotypic females with complete or

partial absence of an X chromosome throughout the body or in a certain number of cells in the body (1). Approximately half of the patients in a TS clinic are expected to have 45,X, while 20-30% are expected to have mosaicism and the remainder are expected to have structural abnormalities of the X chromosome (2). Genotype and phenotype are not perfectly correlated, but in general, patients with mosaicism have a milder course than patients with monosomy X (1). The most important reason for early mortality and morbidity in TS patients is cardiovascular disease (3, 4). TS causes both congenital and acquired diseases of the cardiovascular system (1, 5). There are several factors that increase cardiovascular disease in patients with TS, such as hypertension, dyslipidemia, insulin resistance, congenital heart disease (bicuspid aortic valve (BAV), coarctation of aorta (CoA)), accelerated atherogenesis and ischemic heart disease (4, 6, 7). Cardiovascular risk assessment in TS, especially for aortic dissection (AoD), remains inadequate, due to limited knowledge of the pathophysiology of thoracic aortic disease (8).

Recommendations for the diagnosis of aortic disease in TS include transthoracic echocardiogram (TTE) at diagnosis, followed by imaging of the heart and great vessels by magnetic resonance imaging (MRI) when the child becomes old enough to undergo MRI without general anesthesia. If no abnormality is found, the patient should undergo consecutive MRI every 5 - 10 years (9). Cardiovascular MRI is the gold standard for non-invasive evaluation of cardiovascular disease (10).

Patients with TS, which are thought to have a generalized arteriopathy component, have an increased incidence of AoD compared to the general population (11). In TS, AoD occurs at lower ascending aortic (AA) diameters and at earlier ages than other diseases of the aorta (12, 13). This study aims to evaluate TS patients

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with thorax magnetic resonance angiography (MRA) and measuring their aortic diameters and investigating the correlation of the findings with karyotype.

MATERIALS AND METHODS

Patients and study design

We performed a retrospective evaluation of thorax MRA in 33 TS patients between Jan 2011 and May 2018. Previous medical histories, karyotypes, anthropometric parameters, biochemical results, echocardiogram findings and thorax MRA findings were evaluated.

Each patient was questioned about heart disease, prior cardiac operations, history of hypertension, medications and any other medical problems including hearing defects and renal disease.

The retrospectively collected data, included physical examination, auxological findings, hormone assays, biochemical and radiological findings, additional features at follow-up and surgical and medical treatment. Height and weight were measured by the same auxologist. Body mass index (BMI) was calculated with the formula: $BMI = \text{weight (kg)} / \text{height (m)}^2$. Standard deviation scores (SDS) of these measurements were calculated using national data (14, 15). Haycock formula was used to calculate the body surface area (BSA) (16).

Ambulatory blood pressure measurement was performed for all patients at presentation to screen for hypertension. At follow-up blood pressure was evaluated by a manual sphygmomanometer in the seated position or by review of digital measurements performed at home. Hypertension in children and adolescents was defined as systolic and/or diastolic blood pressure $\geq 95^{\text{th}}$ percentile on repeated measurements (17). Fasting blood glucose (FBG), insulin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels, lipid profile results for total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), triglycerides were recorded. Serum glucose was measured using an automated glucose oxidase method. Insulin levels were measured using an electrochemiluminescent assay. Plasma lipids were measured using an Integra-800 autoanalyzer (Roche). Homeostatic model assessment - insulin resistance index (HOMA-IR) was calculated according to the following formula: $HOMA-IR = [FBG \text{ (mg/dL)} \times \text{insulin level (mIU/L)}] / 405$. HOMA-IR cutoff point for the diagnosis of insulin resistance

is >2.5 in adults and >3.16 in adolescents (18). Serum lipids were evaluated according to national data reported by Can M (19).

Cardiovascular Magnetic Resonance Imaging

An MRI device with the capability to produce 1.5 Tesla Units of magnetic field (Symphony, Siemens Medical Solutions) was used and images were acquired with ECG triggering. T1 weighted spin echo (TR/TE: 700/26; matrix size: 133 x 256; slice thickness: 5 mm), T2- weighted spin echo (TR/TE: 800/81; matrix size: 133 x 256; slice thickness: 5 mm), echo-planar cine true fast images with steady-state precession (50/170; matrix size: 256 x 256; slice thickness: 6 mm) and dark blood (TR/TE 800/26, matrix size: 256 x 256 slice thickness: 6 mm) were obtained. Delayed phase myocardial contrast enhancement was evaluated with 0.1-0.2 mmol/kg of gadolinium based contrast agent, 10-20 minutes after intravenous contrast medium injection. Short and long axis images were obtained on delayed postcontrast phases, (TR/TE: 700/3.3ms; TI: 300ms; flip angle: 25; matrix size: 133x256) with 3D reconstruction and single shot gradient echo sequence (turbo FLASH). Middiastolic diameter of the left ventricle and left ventricular ejection fraction were measured for all patients.

Aortic diameters were measured at five standardized sites, including the sinotubular junction (STJ), AA at the level of the right pulmonary artery, isthmic region (IR), descending aorta (DA) at the level of the left pulmonary artery and abdominal aorta. Standard Z scores of aortic diameters were calculated according to the method defined by Kaiser *et al.* (20). Dilation was defined by a Z-score ≥ 2 . Aortic size index (ASI) was calculated in cm/m^2 by dividing the diameter of the AA by the BSA. The diameter of the aortic sinus was defined as the aortic root diameter. In addition to diameter measurements, the aortic arch, branching anomalies, and venous anomalies were assessed. None of the patients required general anesthesia or sedation during MR imaging.

Echocardiography

Echocardiography was performed using the Vivid 7 ECHO device (General Electric, Milwaukee, WI, USA) with a middle-range frequency (3–8 MHz) broadband transducer in M mode and two-dimensional ECHO (GE Vivid 7) was performed in accordance with the guidelines of the American Society of Cardiology to confirm normal cardiac systolic and diastolic functions.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) for Windows 21.0 was used for statistical analysis. Comparison between study groups (Non 45,X and 45,X) was carried out by parametric (Chi-square test) and non-parametric tests (Mann-Whitney U). Data was reported as mean $\pm$ SD (median). *p* value <0.05 was accepted as statistically significant.

RESULTS

Thirty three patients with TS were included in the study. Mean age at presentation (mean $\pm$ SD) was 9.0 $\pm$ 3.0 years. Fifteen patients were (46%) 45,X, 14 (42%) had mosaicism and 4 (12%) had other chromosomal anomaly. Thorax MRA studies were obtained at 13.7 $\pm$ 3.4 years, at which time the BMI SDS was 0.75 $\pm$ 1.4. The anthropometric measurements of patients are summarized in Table 1.

Mean values for biochemical results including lipid profile, AST and ALT were in normal range. When lipid profiles of patients were evaluated according to the national data (19) three patients had hypercholesterolemia. FBG level was normal however 33% of the patients had IR. IR was controlled with diet, exercise and lifestyle changes and none of the patients required medical treatment.

Four patients (12%) were hypertensive. One patient had undergone surgery for CoA. No patients had AoD. ECHO revealed BAV in five patients (15%), CoA in two patients (6%), prominence of the AA in one patient (3%), and tortuosity of the DA in one patient (3%). MRA revealed cardiac pathology in 10 patients (30%) which were CoA (n=4), aberrant right subclavian artery (ARSA) (n=3), prominence of the AA (n=1), tortuosity of the DA (n=1) and fusiform dilatation of the left subclavian artery (n=1) accordingly. Two of the four patients with CoA found on MRA were detected with ECHO. One patient with CoA was missed on ECHO because of its very distal location. One patient was missed on ECHO due to its mild degree and the consequent lack of a gradient on Doppler imaging. Diameter of the ST junction, which is measured to determine the risk of aortic dilation, was found to be elevated and the mean Z score was above 2.0 [2.4 $\pm$ 1.5; upper - lower limit: 0.35 – 5.7]. Median Z score for the diameter of the isthmus, AA and DA were in normal ranges. Four out of the five patients with BAV had elevated Z scores for aortic diameters (Table 2).

45,X and non-45,X patients were compared with respect to biochemical parameters, aortic diameters and ASI. Mean age, anthropometric data, biochemical results and aortic diameters except for ASI did not differ significantly between the two groups. 45,X patients were found to have significantly higher ASI values (1.7 $\pm$ 0.3

Table 1. Anthropometric data of patients. Variables are expressed as mean $\pm$ SDS (median)

	All patients n=33	45,X n=15	Non 45,X n=18	p
Age (years)	13.7 $\pm$ 3.4 (14.1)	13.3 $\pm$ 3.6 (14.1)	14 $\pm$ 3.3 (14.1)	0.630
Height SDS	-2.5 $\pm$ 1.3 (-2.3)	-2.9 $\pm$ 1.4 (-2.9)	-2.1 $\pm$ 1.1 (-1.9)	0.116
Weight SDS	-0.7 $\pm$ 1.8 (-0.3)	-1.1 $\pm$ 1.9 (-0.9)	-0.4 $\pm$ 1.7 (0.03)	0.338
BMI SDS	0.75 $\pm$ 1.4 (1.1)	-0.6 $\pm$ 1.4 (1.0)	0.9 $\pm$ 1.4 (1.1)	0.561
Waist Circumference SDS	1.6 $\pm$ 1.4 (1.9)	1.0 $\pm$ 1.6 (1.7)	2.2 $\pm$ 1.0 (2.4)	0.065
Cholesterol (mg/dL)	174.2 $\pm$ 28 (170)	169.8 $\pm$ 29.6 (165)	177.6 $\pm$ 27 (170)	0.509
LDL (mg/dL)	91.3 $\pm$ 24.5 (88.5)	86.1 $\pm$ 23.8 (85)	95.1 $\pm$ 25 (89.8)	0.478
Triglycerides (mg/dL)	95.4 $\pm$ 45 (82.5)	105.6 $\pm$ 45.3 (92)	87.5 $\pm$ 44.4 (77.5)	0.193
VLDL (mg/dL)	18.8 $\pm$ 9.4 (16)	21.1 $\pm$ 9.3 (19.8)	17 $\pm$ 9.4 (15)	0.133
HDL (mg/dL)	64.1 $\pm$ 15.5 (62.2)	58.5 $\pm$ 15.7 (61)	68.6 $\pm$ 14.3 (67)	0.173
HOMA-IR	2.6 $\pm$ 1.7 (2.3)	2.3 $\pm$ 1.8 (1.7)	2.8 $\pm$ 1.6 (2.4)	0.29

SDS, standard deviation score; BMI, body mass index; LDL, low density lipoprotein; VLDL, very low density lipoprotein; HDL, high density lipoprotein; HOMA-IR, Homeostatic model assessment - insulin resistance index.

Table 2. Aortic diameters of TS patients with BAV

Patient	Karyotype	Cardiac problem	Aortic diameter*	ASI (cm/m ²)
1	45,X	CoA	ST Z score 3.8 DA Z score 2.6	2.2
2	45,X	-	AA Z score 2.2	2.2
3	Non 45,X	-	ST Z score 2.9	1.4
4	45,X	Minimal AI ARSA	ST Z score 3.8 Isthmus Z score 2.1	1.9
5	Non 45,X	-	N	1.5

* largest aortic diameter in measurements. CoA Coarctation of the aorta, ASI aortic size index, ST sinotubular junction, DA descending aorta, AA ascending aorta, AI aorta insufficiency, ARSA aberrant right subclavian artery.

Table 3. Aortic diameter measurements and Z scores of patients. Variables are expressed as mean±SDS (median)

	All patients	45,X	Non45,X	p
ST Z score	2.4±1.7 (2.6)	2.5±1.5 (2.9)	2.3±1.7 (2.1)	0.780
AA (mm)	20.4±3 (20.0)	20.4±2.6 (21.7)	20.3±3.4 (19.6)	0.866
AA Z score	0.28±1.2 (0.4)	0.57±1.1 (0.64)	0.01±1.3 (-0.21)	0.129
Aortic arch (mm)	16.6±2.6 (17)	16.7±2.5 (17)	16.6±2.8 (16.5)	0.779
Aortic isthmus Z score	0.82±1.5 (0.9)	1.2±1.2 (1.0)	0.52±1.7 (0.66)	0.244
DA (mm)	14.8±2.1 (14.7)	15.0±2.3 (14.8)	14.6±2.0 (14.5)	0.808
DA Z score	-0.2 ±1.2 (-0.4)	0.1±1.1 (-0.3)	-0.5±1.15 (-0.7)	0.163
Abdominal aorta (mm)	12.9±2.3 (12.9)	13.4±2.5 (14)	12.4±2.1 (12)	0.261
ASI	1.6±0.3 (1.5)	1.7±0.3 (1.6)	1.5±0.3 (1.4)	0.036

ST sinotubular junction, AA ascending aorta, DA descending aorta, ASI aortic size index.

and 1.5±0.3, p=0.036). The measurements of aortic dimensions and Z scores are summarized in Table 3.

DISCUSSION

The prevalence of congenital heart disease in TS is 23 - 50% (9, 21). Twenty five percent of Turkish TS patients have been reported to have cardiovascular anomalies (22). Conventionally, the most common type of anomaly in TS is accepted to be obstructive lesion of the left side of the heart, namely bicuspid aortic valve (BAV), coarctation of aorta (CoA), aortic stenosis and hypoplastic left heart and Turkish reports state similar findings (9, 21, 22). In our study, the most common cardiac anomaly was BAV. CoA was found to be the second most common anomaly. In keeping with existing literature, we support the notion that the occurrence of BAV or CoA in a female should be considered as a marker of TS and should prompt an evaluation of the karyogram (21, 23).

Having a BAV substantially increases the risk

of aortic dissection (AoD), and its identification is extremely important (24). CoA affects 12% of patients with TS and is present in 89% of patients who have AoD. CoA is usually diagnosed in infancy, but it may be diagnosed later in childhood following the detection of hypertension. ECHO is the initial screening investigation and should be performed at diagnosis (1). In a study conducted by the National Institutes of Health evaluation of thoracic MRA in addition to ECHO is suggested because MRA revealed additional anomalies (25). In the present study, ECHO revealed BAV in five patients who were underdiagnosed by MRA, because the resolution provided by the section thickness on MRA was 4 mm. On the other hand, MRA revealed four patients of CoA, two of them were missed on ECHO. One patient with CoA was missed on ECHO because of its very distal location. One patient was missed on ECHO due to its mild nature and the consequent lack of a gradient on Doppler imaging. The current guideline recommends that thoracic MRA would be obtained in every patient with TS as soon as the patient is old

enough to undergo the procedure without sedation and that thereafter the MRA would be repeated once every 5-10 years (1). In light of our findings, we also suggest that the first investigation to view the heart of a TS patient would be ECHO, followed by MRI obtained as soon as it can be tolerated without sedation.

AoD is six times more common in TS than in the general population, with an incidence of 40 cases per 100 000 TS years (5, 26, 27). AoD occurs earlier and at lower ascending aorta (AA) diameters in TS than other genetic diseases of the aorta (27, 28). Although AoD is infrequent in the children with TS, screening of all TS patients from early childhood onward for hypertension and prompt treatment may decrease the risk of AoD (29). Hypertension has been found to be related to aortic dilation and AoD in patients with TS (30). Consequently, TS patients require tight blood pressure control to decrease the risk of aortic dilation. TS is known to be commonly associated with such atherosclerosis risk factors as obesity and atherogenic lipid profile (7, 22, 31-33). The most common reasons for early mortality and morbidity in TS are cardiovascular and cerebrovascular disorders that result from premature atherosclerosis (29). Twenty two percent of our patients were obese, 12% of patients were hypertensive and 9% of patients were dyslipidemic. None of the patients had AoD. We recommend close surveillance of TS patients for the development of metabolic syndrome. Blood pressure should be regularly measured in every patient with TS, and that patients with hypertension should undergo more frequent cardiac evaluation.

Aortic dilation affects 19% of children and adolescents with TS and can start from six years of age. Predisposing factors for aortic dilation are congenital heart defects and hypertension, which are common in TS. However, some patients with TS with aortic dilation have no other risk factors except for TS itself (34). Nevertheless, ECHO has been shown to have lower sensitivity for detecting aortic dilation in TS than MRI, occasionally missing both pediatric and adult patients. In addition, ECHO may not adequately visualise the thoracic aorta, which is important because dilation may also affect the descending aorta (DA), where approximately 20% of dissections occur. It is reported that the aortic diameters and Z-scores of both the AA and DA aorta were higher in the presence of BAV, which suggests that patients with BAV are at greater risk for aortic dilation and its complications (24, 35). Hahn *et al.* have reported a high prevalence of aortic root dilation in patients with BAV (35). Mortensen *et*

al. evaluated 80 TS patients and found that the presence of BAV is associated with a progressive increase in the diameter of the aortic sinus (8). However, some studies do not demonstrate this association between BAV and aortic dilation. Carlson *et al.* reported that individuals with TS and BAV experience AoD at a younger age and at considerably smaller aortic diameters than those who develop AoD in the general population (27). Previous studies have suggested that a risk is better predicted by relative aortic size rather than absolute aortic size; therefore, correction of the aortic diameter for the calculated body surface area (BSA) has been proposed (36). The absence of BAV appears to markedly reduce, but not eliminate the risk of AoD (27). In our study, five patients had BAV, four of whom had dilation at various levels of the aorta. Moreover, two of these patients had a high aortic size index (ASI). These findings suggest that BAV increases the risk of aortic dilation and warrants close follow-up for its complications.

Using MRI, the AA diameters are normalised to BSA to give the ASI and based on data ASI is used to predict AoD risk in TS patients. The 95th percentile equates to an ASI >2.0 cm/m², indicating that dilation is present and requiring annual MRI and tight blood pressure control. The 99th percentile equates to an ASI >2.5 cm/m², which should alert urgent evaluation for intervention and a surgical consult. ASI >2.5 cm/m² appears to predict AoD risk in adults with TS (28). However, Quezada *et al.* (37) reported that in their healthy subjects between the ages of 2 and 15 years ASI was >2.5 cm/m². If the ASI is <2 cm/m² in the presence of risk factors for AoD, the patient should be considered at moderate risk, and MRI should be considered every three years to detect any change in aortic diameter. If no risk factors for AoD are present and no baseline dilation is seen (ASI <2 cm/m²), repeat imaging is warranted at transition, given that dilation can occur even in the absence of predisposing factors. Yiğit *et al.* (24) reported that the Z-score of the AA in 28.3% of the patients and the Z-score of the DA in 15.2% of the patients were >2 in their cohort, which indicated aortic dilation. In that study, an ASI higher than 2 cm/m², which reflects dilation of the AA, was detected in 28.3% of the patients and ASI higher than 2.5 cm/m², which is considered as a high risk factor for AoD, was observed in 4 (8.7%) patients. ASI >2.5 cm/m² was associated with BAV. ASI is useful in adult populations where BSA is relatively constant (28, 36). In our study, the mean ASI was 1.6±0.3cm/m². Two patients with BAV had increased ASI. Patients that had

45,X karyograms had higher ASI values than the non-45,X patients. In conclusion, 45,X patients and patients with BAV should be followed closely for secondary complications.

The main limitations of the present study were the relatively small number of patients and the absence of a healthy control group, which were a result of the fact that this was a single center study for an uncommon disease. The fact that Z scores were calculated according to the data of a single study (20) was another limitation. Further studies are needed to validate the normal ranges of the aortic diameters in the pediatric population.

In conclusion, although aortic dissection does not usually occur during childhood, because hypertension increases the risk of aortic dissection, frequent evaluation of patients with Turner syndrome for hypertension from early childhood onward may decrease the risk of aortic dissection. We conclude that Turner syndrome patients with bicuspid aortic valve are at higher risk for aortic dilation and 45,X patients have higher aortic size index values and therefore are at higher risk of secondary complications. Thorax magnetic resonance angiography seems to be warranted in patients with Turner syndrome to detect additional anomalies of the heart and great vessels.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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