J Pediatr Res
DOI: 10.4274/jpr.galenos.2018.63439

Original Article

The Role of Cardiac Magnetic Resonance İmaging in Determination of Cardiyovascular Anomalies in Children and Young Adults with Turner Syndrome

Özlem Korkmaz[1], Recep Savaş[2], Ertürk Levent[3], Samim Özen[1], İlkin Mecidov[1], Damla Gökşen[1], Şükran Darcan[1]

[1]Ege University Faculty of Medicine, Department of Pediatric Endocrinology and Diabetes, İzmir, Turkey
[2]Ege University Faculty of Medicine, Department of Radiology, İzmir, Turkey
[3]Ege University Faculty of Medicine, Department of Pediatric Cardiology, İzmir, Turkey

ABSTRACT

Aim: Congenital cardiovascular anomalies and aortic dilatation are common in patients with Turner syndrome. The aim of this study was to compare echocardiography findings with cardiovascular anomalies and aortic dilatation identified using magnetic resonance imaging in children and young adults with Turner syndrome.

Materials and Methods: Twenty-six girls with TS aged 11-20 years were recruited through tertiary centers. Cardiovascular anomalies and aortic diameter were evaluated using cardiovascular magnetic resonance imaging (CVMR). Auxological measurements, karyotype analyses, medical therapies (growth hormone, estrogen, and thyroid replacement therapy) and transthoracic echocardiography findings were recorded for all participants.

Results: Normal cardiac anatomy was identified in 16 (61.5%) of our 26 cases, with no cardiac pathology being identified at either CVMR or echocardiography. Cardiovascular anomalies were identified in 5 of the 26 (19.2%) patients at CVMR. Aortic dilatation was determined in four patients (one with descending and ascending aorta, one with ascending aorta, and two with descending aorta). Aortic size index was < 2 cm/m^2 in all patients. Echocardiography was normal for the three patients with malformation detected at CVMR.

Conclusion: CVMR identifies significant cardiac lesions missed by echocardiography in pediatric patients with Turner syndrome, especially aortic dilatation and other vascular anomalies.

Keywords: Turner Syndrome, cardiac magnetic resonance imaging, cardiovascular anomalies

Introduction

Turner syndrome, or monosomy X, is caused by complete or partial absence of one of the two normal X-chromosomes (1). It affects one in 2000 live-born females. The most serious clinical aspect of the syndrome is due to congenital and/or acquired cardiovascular diseases. Cardiovascular morbidity has been estimated to affect approximately 50% of patients with Turner syndrome. Cardiovascular anomalies include bicuspid aortic valve (BAV), persistent left superior vena cava, anomalous pulmonary venous return, elongation of the transverse aorta, coarctation of the aorta, aortic dissection, and dilatation and pseudocoarctation of the aorta (2,3,4). However, the syndrome has also been associated with other arterial and venous anomalies. The incidence of cardiovascular lesions ranges from 23% to 45% (3,5). Mortality rates are three times higher in women with Turner syndrome than in the normal female population (1). Shortened lifespan is often due to cardiovascular complications, such as aortic dilatation and dissection (6). Transthoracic echocardiography (ECHO) and cardiovascular magnetic resonance imaging (CVMR) are the principal methods used for the diagnosis and surveillance

Address for Correspondence
Özlem Korkmaz MD, Ege University Faculty of Medicine, Department of Pediatric Endocrinology and Diabetes, İzmir, Turkey
Phone: +90 232 390 12 30 E-mail: ozlem-korkmazz@hotmail.com ORCID ID: orcid.org/0000-0001-9093-6205
Received: *28.11.2018* **Accepted:** *28.12.2018*

of these conditions (7). A high prevalence of structural anomalies in patients with Turner syndrome that are not suspected at ECHO has been detected using CVMR. Although ECHO is a standard method for evaluating cardiac anatomy in Turner syndrome patients, its usefulness in the evaluation of vascular anomalies is limited. CVMR is recommended for the management of patients with Turner syndrome (7,8,9). The aim of this study was to compare ECHO findings with cardiovascular anomalies and aortic dilatation identified using magnetic resonance imaging in children and young adults with Turner syndrome.

Materials and Methods

Twenty-six girls and women with Turner syndrome aged 11-20 years were enrolled in this study. Subjects able to tolerate CVMR without sedation were included, and patients <11 years were therefore excluded. Relevant clinical data, including auxological measurements (weight, weight SDS, height, height SDS, BMI, and BMI SDS), karyotype analyses, and medical therapies (growth hormone, estrogen, and thyroid replacement therapy) were recorded. Body surface area (BSA) was calculated based on the formula described by Dubois & Dubois (10). ECHO findings were recorded retrospectively. The study was approved by our faculty ethical committee.

Magnetic Resonance Imaging

All patients underwent imaging on a 3 Tesla magnetic resonance scanner (Verio, Siemens Medical Systems) using a body coil and included axial T2 weighted HASTE sequences. Magnetic resonance angiography was conducted with flash 3D coronal images and 0.2mmol/kg of Gadolinium-chelate contrast media administered through an antecubital vein with a magnetic resonance compatible injector (Ulrich, Germany). Post gadolinium axial T1W VIBE images also were performed. The diameters of the ascending and descending aorta were measured on axial T1-weighted images at the level of the right pulmonary artery, perpendicular to the long axis of the ascending aorta in a blinded fashion.

All participants tolerated CVMR without sedation or complications. Measurements were recorded for ascending and descending aortic diameter and pulmonary conus diameter, and aortic size index (ascending aorta /body surface area). Measurements were standardized by BSA to determine Z scores. The aorta and pulmonary conus were considered dilated in case of a Z score greater than 2. Aortic size index (ASI) values were also calculated (cm/m2). Aortic coarctation, transverse arch, bovine arch, left vertebral artery anomaly, aberrant right subclavian artery, persistent left superior vena cava, partial pulmonary venous return anomaly were recorded.

Statistical Analysis

Descriptive statistics were used for data analysis. Continuous data were expressed as mean values with ranges. Z scores were calculated for weight, height, and BMI, and represented as mean values (±standard deviation). The frequencies of vascular anomalies and cardiac lesions were analyzed, and any disparity between ECHO and CVMR findings was noted.

Results

Twenty-six girls with Turner syndrome, aged 11-20 years of age, were included in the study. Mean age at investigation was 16.6 ± 2.8 years. The patients' clinical characteristics are shown in Table 1. Karyotype analysis revealed 57.7% (n:15) 45,X monosomy, 30.8% (n:8) mosaicism, and 11.5% (n:3) isochromosome. In terms of treatment, 84.4% (n:23) of the patients received growth hormone therapy. Normal cardiac anatomy was identified in 16 of 26 (61.5%) had a cardiac pathology identified on either CVMR or ECHO. Cardiovascular anomalies were identified in five of the 26 (19.2%) patients at CVMR. Of these, 45,X monosomy karyotypes were identified in four and 46,X,i(Xq) in one. CVMR revealed pseudocoarctation in two patients, aberrant right subclavian artery in two, and azygos lobe fissure variations in one. An appearance compatible with bicuspid aorta was identified at ECHO in one case in which pseudocoarctation was detected at CVMR and in one patient with right aberrant subclavian artery detected at CVMR. ECHO was normal for the other three patients with malformation detected at CVMR. CVMR was normal in two cases in which ASD secundum was detected at ECHO.

Mean ±standard deviation of ascending aortic diameter 2.16±0.29 cm and Z score 0.08±1.4, descending aortic diameter 1.63±0.30 cm and Z score -0.07±1.34, and pulmonary conus

Table I. Clinical characteristics of study participants with Turner Syndrome

Age at investigation (year)	16.6±2.8
Weight SDS	-0.06±1.33*
Height SDS	-1.96±1.14*
BMI SDS	1.24±0.99*
BSA (m2)	1.48(1.30-1.58)*
45,X monosomy	15/26 (57.7%)**
Mosaicism	8/26 (30.8%)
Isochromosome	3/26 (11.5%)
Growth hormone therapy	23/26 (88.4%)**
Estragen-replacement therapy	22/26 (84.6%)**
Thyroid –replacement therapy	4/26 (15.3%)**

*Variables are represented as means±standard deviation, **Caterogical variables are represented as frequencies (%)

diameter 1.91 ± 0.47 cm and Z score -0.94 ± 1.59 were detected. The mean±standard deviation ASI was 1.44 ± 0.24 cm/m^2. Aortic dilatation was determined in four patients (15.3%) in our study (one with descending and ascending aorta, one with ascending aorta, and two with descending aorta). ASI was < 2 cm/m^2 in all patients.

Discussion

CVMR is the gold standard method for the diagnosis and follow-up of thoracic aorta morphological anomalies in patients with Turner syndrome (7). Transthoracic ECHO may be of limited use in assessing anatomy in the abnormally shaped chest, and can underestimate the size of both the ascending and descending aorta in patients with Turner syndrome. Although CVMR is clearly recommended in the guidelines, the optimal timing of the first imaging is not well established. CVMR is used in older girls and adults who are able to tolerate the procedure without sedation. Subsequent routine imaging is recommended every 5-10 years (11). Patients over 10 years of age and evaluated with MRI without the need for sedation were included in our study group.

Growth hormone deficiency is associated with increased cardiovascular risk (12). Growth hormone and the 45,X monosomy karyotype are correlated with a dilated proximal aorta (13). Donadille et al. (14) emphasized that patients with monosomy X in the cohort study should be monitored more closely in cardiovascular terms. Karyotype analysis revealed 45,X monosomy in four of the five patients with cardiac anomaly detected at CVMR and in all four patients with enlarged aortic diameter. Except for one patient in whom aberrant right subclavian artery anomaly was detected, all cases were treated with growth hormone.

Pseudocoarctation of the aortic arch is a rare congenital anomaly which resembles true coarctation and is caused by the presence of a narrowing in the descending thoracic aorta immediately distal to the origin of the left subclavian artery (15). In our study, pseudocoarctation was detected in two cases at cardiac MRI, but this finding was not detected using ECHO in one case.

Ho et al. (2) estimated a prevalence of aberrant right subclavian artery frequency in Turner syndrome of 8%, compared to 0.4-2% in the normal population (16). In our study, an aberrant right subclavian artery anomaly was detected with CVMR in two cases. BAV is also common Turner syndrome (17). In their comparison of CVMR and ECHO, Ostberg et al. (8) demonstrated an 18% prevalence of BAV based on ECHO findings (CVMR data were not shown). BAV has been determined in 1.5-17.5% of children and adults with Turner syndrome using CVMR and ECHO (3,4). Bicuspid aorta was determined in three patients at ECHO in our study. None of these patients exhibited valve pathology at CVMR.

A greater incidence of interrupted inferior vena cava with azygos continuation has also been reported in patients with Turner syndrome (3,4). A variation of azygos lobe fissure was detected in one patient at MRI in our study.

It is generally agreed that patients with Turner syndrome have a significantly elevated risk of aortic dissection. The few risk factors described include hypertension, the presence of BAV or coarctation, and dilatation of the aorta (8,18). Dilatation of the aorta in certain anatomical locations has been associated with an increased risk of dissection. Castro et al. (19) CVMR study of children and young adults with Turner syndrome reported aortic dilatation in 26.7% of patients. Another pediatric study reported an incidence of aortic dilatation of 37% in Turner syndrome patients (13). In a study of children and young adults with Turner syndrome by Yiğit et al.(20), CVMR and 3D contrast-enhanced MRI angiography revealed incidences of BAV of 19.6%, coarctation of 6.5%, ascending aorta dilatation of 28.3% and descending aorta dilatation of 15.2%. BAV was identified as an important risk factor for aortic dilatation. In another study, possession of the 45,X karyotype and BAV predicted dilatation of the ascending aorta, but dilatation of the descending aorta was only observed in patients with coarctation (21). In our study, one patient with a dilated aortic diameter had a bicuspid aortic appearance at ECHO. Karyotype analysis was 45,X monosomy in all cases in which we detected aortic dilatation. The ASI is a method used to evaluate the degree of aortic disease. A ratio of 2 cm/m2 requires close follow-up, while values >2.5 cm/m2 require transfer to an experienced center. ASI >2cm/m2 is considered to represent an absolute

Table II. Comparison of CVMR findings with echocardiography

CVMR		Echocardiography	
Findings	**n**	**Findings**	**n**
Aberran right subclavian artery	2	Bicuspid aorta Normal	1 1
Pseudocoarctation	2	Bicuspid aorta Normal	1 1
Azygos lobe fissure varyation	1	Normal	1
Aortic dilatation	4	Bicuspid aorta Normal	1 3
Normal	17	Secundum ASD	2

CVMR: Cardiovascular magnetic resonance, ASD: Atrial septal defect

Table III. CVMR imaging measurement data of study group

	Mean±standard deviation	z-score
Ascenden aort diameter (cm)	2.16±0.29	0.08±1.4
Descenden aort diameter (cm)	1.63±0.30	-0.07±1.34
Pulmonary conus diameter (cm)	1.91±0.47	-0.94±1.59
Aortic size index (cm/m^2)	1.44±0.24	

contraindication for pregnancy (22,23). ASI values were < 2 cm/m2 in all our patients.

One of the limitations of our study was the small sample size. Further research with large patient series, especially in the pediatric age group, is now needed. Second limitation, breathing and cardiac artefacts may have prevented the correct viewing of the CVMR.

Conclusion: CVMR should be performed on patients with Turner syndrome even if ECHO reveals a normal cardiac anatomy. CVMR can identify significant cardiac lesions missed by ECHO in pediatric patients with Turner syndrome, especially aortic dilatation and other vascular anomalies. Early diagnosis and institution of preventative and medical measures are critical for preserving quality of life and lifespan in Turner syndrome patients.

Ethics

Ethical Committee Approval: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimetation (Ege University) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of Ege University (approval number: 18-7.1/31).

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

Financial Support: This research received no spesific grand from any funding agency or from commercial or not for profit sectors.

References

1. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF & Jacobs PA. Mortality in women with turner syndrome in Great Britain: a national cohort study. Journal of Clinical Endocrinology and Metabolism 2008; 93: 4735–42.
2. Ho VB, Bakalov VK, Cooley M, et al. Major vascular anomalies in Turner syndrome: prevalence and magnetic reso-nance angiographic features. Circulation 2004; 110: 1694–700.
3. Dawson-Falk KL, Wright AM, Bakker B. et al. Cardiovascular evaluation in Turner syndrome: utility of MR imag-ing. Australasian Radiology 1992; 36: 204–9.
4. Kim HK, Gottliebson W, Hor K. et al. Cardiovascular anomalies in Turner syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young adult population.AJR. American Journal of Roentgenology 2011;196: 454–60.
5. Mazzanti L, Cacciari E. Congenital heart disease in patients with Turner's syndrome: Italian Study Group for Turner Syndrome (ISGTS). J Pediatr 1998; 133: 688–92.
6. Gravholt C, Landin-Wilhelmsen K, Stochholm K, et al. Clinical and epidemiological description of aortic dissection in Turner's syndrome. Cardiology in the Young 2006; 16: 430–6.
7. Mortensen KH, Gopalan D, Norgaard BL, Andersen NH, Gravholt CH. Multimodality cardiac imaging in Turner syndrome. Cardiol Young 2016 ;26:831-41.
8. Ostberg JE, Brookes JA, McCarthy C. A comparison of echocardiography and magnetic resonance imaging in cardiovascular screening of adults with Turner syndrome. Journal of Clinical Endocrinology and Metabolism 2004; 89:5966-71.
9. K.H. Mortensen, B.E. Hjerrild, K. Stochholm. Dilation of the ascending aorta in Turner syndrome - a prospective cardiovascular magnetic resonance study .Journal of Cardiovascular Magnetic Resonance 2011; 28:13-24.
10. Dubois D & Dubois E. A formula to estimate the approximate surface area if eight and weight be known. Archives of Internal Medicine 1916; 17:863–71.
11. Bondy, C.A. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. Journal of Clinical Endocrinology and Metabolism 2007; 92:10–25.
12. Stochholm K, Laursen T, Green A, et al. Morbidity and GH deficiency: a nationwide study. Eur J Endocrinol 2008;158:447–57.
13. Somerville S, Rosolowsky E, Suntratonpipat S, Girgis R, Goot BH, Tham EB. Cardiac Magnetic Resonance Imaging in Pediatric Turner Syndrome . J Pediatr 2016;175:111-5.
14. Donadille B, Rousseau A, Zenaty D. Cardiovascular findings and management in Turner syndrome: insights from a French cohort European Journal of Endocrinology 2012;167: 517–22.
15. Klein LW, Levin JL, Weintraub WS, Agarwal JB, Helfant RH. Pseudocoarctation of the aortic arch in a patient with Turner's syndrome. Clin Cardiol 1984 ;7:621-3.
16. Freed K, Low VHS. The aberrant subclavian artery. AJR Am J Roentgenol 1997; 168: 481–4.
17. Iris Gutmark-Little, Philippe F. Backeljauw. Cardiac magnetic resonance imaging in Turner syndrome. Clinical endocrinology 2013; 78:646-58.
18. Matura LA, Ho VB, Rosing DR. et al. Aortic dilatation and dissection in Turner syndrome. Circulation 2007;116:1663–70.
19. Castro AV, Okoshi K, Ribeiro S.M. et al. Cardiovascular assessment of patients with Ullrich-Turner's Syndrome on Doppler echocardiography and magnetic resonance imaging. Arquivos Brasileiros de Cardiologia 2002; 78:51–8.
20. Yiğit H, Önder A, Özgür S, Aycan Z, Karademir S, Doğan V. Cardiac MRI and 3D contrast-enhanced MR angiography in pediatric and young adult patients with Turner syndrome. Turk J Med Sci. 2017; 47:127-33.
21. Mortensen KH, Hjerrild BE, Andersen NH et al. Abnormalities of the major intrathoracic arteries in Turner syndrome as revealed by magnetic resonance imaging. Cardiology in the Young 2010; 20:191–200.
22. Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. Circulation 2007; 116:1663-70.
23. Nijs J, Gelsomino S, Lucà F, Parise O, Maessen JG, Meir ML. Unreliability of aortic size index to predict risk of aortic dissection in a patient with Turner syndrome. World J Cardiol 2014; 6: 349–52.