

## Cardiac MRI and 3D contrast-enhanced MR angiography in pediatric and young adult patients with Turner syndrome

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**Background/aim:** This study aimed to describe the spectrum and frequency of cardiovascular abnormalities in pediatric and young adult patients with Turner syndrome (TS) using cardiac MRI and MR angiography.

**Materials and methods:** This prospective study consisted of 47 female patients of pediatric age and young adults with a karyotypically confirmed diagnosis of TS. All patients underwent cardiac MRI and contrast-enhanced MR angiography. A second examination after 9–26 months was performed for 28 of these patients.

**Results:** Elongation of the transverse aortic arch (ETA) was the most frequent abnormality with a rate of 37%. The rate of partial anomalous pulmonary venous connection (PAPVC) was 21.7%, bicuspid aortic valve (BAV) was 19.6%, coarctation was 6.5%, ascending aorta dilatation was 28.3%, and descending aorta dilatation was 15.2%. The diameters of the aorta and the rate of aortic dilatation per unit of time was greater in the patients with BAV ( $P < 0.05$ ). ETA was less observed in the patients who were receiving growth hormone therapy ( $P < 0.05$ ).

**Conclusion:** The most common cardiovascular abnormalities in TS patients are aortic arch anomalies such as ETA and coarctation, aortic dilatation, PAPVCs, and BAV. The presence of BAV is an important risk factor for the aortic dilatation.

**Key words:** Ullrich–Turner syndrome, cardiovascular system, aortic arch, magnetic resonance imaging, magnetic resonance angiography

### 1. Introduction

Turner syndrome (TS) is a genetic disorder characterized by the loss of all or a part of one of the sex chromosomes, and it occurs in 1 in 2500 live-born females (1,2). In these patients, cardiovascular assessment and follow-up are important as complications can be life-threatening. Transthoracic echocardiography (TTE) is the primary examination method for assessing these patients, while cardiac MRI and MR angiography are used as supplementary methods (3–8). There are many MRI studies of adult TS patients; however, those addressing pediatric and young adult patients are quite limited (8–11). The current study carried out cardiac MRI and MR angiography in pediatric and young adult patients with TS.

### 2. Materials and methods

The study included 47 female pediatric or young adult patients with a karyotypically confirmed diagnosis of TS. The detailed medical history of the participants was

recorded and anthropometric assessments were performed. All patients underwent cardiac MRI and contrast-enhanced MR angiography. A second examination after 9–26 months (mean interval: 16.6 months) was performed in 28 of these patients to compare changes in measurements per unit of time. This prospective study was approved by the institutional review board and written informed consent was obtained from all patients.

#### 2.1. Cardiac MRI and MR angiography

Magnetic resonance examinations were performed at 1.5 T (Signa HDi, GE Healthcare, Milwaukee, WI, USA). An eight-channel torso surface coil (8-ch Body Array; Invivo Corporation, Gainesville, FL, USA) was used for all data acquisition. None of the patients required sedation or anesthesia.

Cardiac functional and morphological assessments were made using balanced steady-state free precession (b-SSFP) sequences. Cine images of the following views were obtained: two-, three-, and four-chamber long-axis

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views; a short-axis stack from the cardiac base to apex; a coronal left ventricular outflow tract view; axial sections through the aortic valve plane; and double-oblique sagittal candy-cane stack for the aortic view. Additionally, straight axial sections, starting at the supraaortic level and covering the entire heart, were obtained to reveal cardiac and vascular anatomy. Furthermore, through-plane cine phase-contrast flow imaging was performed above and at the aortic valve plane, and at coarctation level when applicable.

Three-dimensional MR angiography was performed in coronal or oblique coronal 3D spoiled gradient-echo pulse sequences before and after contrast injection. A single dose (0.1 mmol/kg) of gadolinium-based contrast medium was administered i.v. using a power injector. The exact timing of MR angiography was achieved using automated bolus detection and acquisition triggering software (Smartprep, GE Medical Systems).

The imaging parameters of used sequences are listed in Table 1.

## 2.2. Image analysis

Image analysis was performed on a remote workstation (Advantage Windows, version 4.3; GE Medical Systems) by one radiologist who had 5 years of experience in cardiovascular MR imaging.

Cardiac measurements and functional assessments were made using cardiac analysis software (ReportCard 2.0; GE Medical Systems). The aortic valve area was measured in axial images obtained from the aortic valve plane. Maximum velocities were measured via phase-contrast velocity-encoded cine MR imaging, and the pressure gradient ( $\Delta P$ ) was estimated using the modified Bernoulli's equation  $\Delta P = 4(v^2)$  (12). In patients with aortic regurgitation, the regurgitant volume and regurgitant fraction were calculated.

During MR angiography, source images, subtraction images, 2D multiplanar reconstructed (MPR) images, and 3D maximum intensity projection (MIP) angiograms were

interpreted. Diameter measurements were performed on oblique MPR images, which were obtained perpendicular to the centerline of the vessel. The diameter of the ascending aorta at the level of the right pulmonary artery was defined as the ascending aortic diameter, whereas the diameter of the descending aorta at the same level was defined as the descending aorta diameter. The diameter of the aortic sinus was defined as the aortic root diameter. A standardized Z-score was calculated for the ascending and descending aorta according to the method defined by Kaiser et al. (13). Aorta diameter and body surface area (BSA) were used and the Z-score was calculated by subtracting the measured diameter from the predicted diameter and dividing by the SD of residuals. In addition, the ratio of the ascending aorta diameter at the level of the right pulmonary artery to the diameter of the descending aorta at the same level was calculated for each patient (AD/DD). Furthermore, the aortic size index (ASI), indexing the ascending aorta directly with the BSA, was calculated.

In addition to diameter measurements, the aortic arch, branching anomalies, and venous anomalies were assessed. Elongation of the transverse aortic arch (ETA) was defined as the presence of a posterior origin of the left subclavian artery behind the trachea on axial images and an inward indentation or convex kinking of the inferior aortic contour along the lesser curvature (14).

BSA-corrected index values were used for all measurements and calculations. BSA was determined by the Mosteller formula (15). Intracardiac areas were indexed directly by BSA. Since linear dimensions and volumes had a nonlinear relation to BSA, they were indexed using BSA to the power 0.5 and 1.5, respectively (16,17).

## 2.3. Statistical analysis

Associations between categorical and quantitative variables were analyzed using one-way ANOVA, whereas associations between categorical variables were analyzed using Pearson's chi square ( $\chi^2$ ) test and Fisher's exact test. Statistical significance was set at  $P < 0.05$ . Statistical

**Table 1.** Imaging parameters in cardiac MRI and MR angiography sequences.

Parameter	Cine b-SSFP*	Phase-contrast flow imaging	MR angiography
Sequence	2D FIESTA	Fast 2D PC	3D FSPGR
TR (ms)/TE (ms)	3.4–3.9/1.5–1.7	7–7.8/4–4.7	3.5–3.7/1.3–1.4
Flip angle (°)	55	25–30	30
Slice thickness (mm)/gap (mm)	6–8/0	6–8/0	3.6/–2.7
FOV (cm <sup>2</sup> )	30–31	29–31	32
Matrix	256 × 200	192 × 128	352 × 224

\*b-SSFP: Balanced steady-state free precession.

analysis was performed using Predictive Analytics Software version 18 (PASW 18, SPSS, Chicago, IL, USA).

### 3. Results

It should be taken into account that all data given in this section are BSA-corrected data, indexed by BSA to the power of 0.5, 1.0, or 1.5 for linear dimensions, areas, and volumes, respectively.

#### 3.1. Clinical data

The mean age of patients was 14.3 years (age range: 7–22 years). The clinical data of the patients are summarized in Table 2.

#### 3.2. Aortic arch and branching anomalies

The rate of ETA was 37% (Figure 1). Of ETA components, an inferior kink was observed at a rate of 56.5%, and subclavian late takeoff at a rate of 58.7%. Flattening on the transverse arch was found at a rate of 52.2%. Coarctation was found in three (6.5%) patients.

ETA was observed less frequently in patients receiving growth hormone (GH) therapy (5/25) compared to patients who were not (13/22;  $P < 0.05$ ). Flattening at the aortic arch and late takeoff of the subclavian artery were also observed less frequently in patients who were receiving GH therapy (8/26, 11/26, respectively) compared to those who were not (16/21, 16/21, respectively;  $P < 0.05$ ).

Mean aortic valve area was lower in patients with ETA ( $158.08 \pm 42.82 \text{ mm}^2/\text{BSA}$ ) compared to those without ETA ( $178.34 \pm 22.66 \text{ mm}^2/\text{BSA}$ ;  $P < 0.05$ ). Mean Z-score for the descending aorta was higher in the patients with an inferior kink ( $1.33 \pm 1.37$ ) compared to those without the same ( $0.60 \pm 0.87$ ;  $P < 0.05$ ). Mean Z-score and diameter of the ascending aorta were higher in patients with late

takeoff ( $2.16 \pm 2.51$ ,  $21.63 \pm 4.76 \text{ mm}/\text{BSA}^{0.5}$ , respectively) compared to those without the same ( $0.91 \pm 1.07$ ,  $19.17 \pm 1.89 \text{ mm}/\text{BSA}^{0.5}$ , respectively) and with flattened arch ( $2.23 \pm 2.61$ ,  $21.75 \pm 4.93 \text{ mm}/\text{BSA}^{0.5}$ , respectively) compared to those without the same ( $1.01 \pm 1.15$ ,  $19.37 \pm 2.13 \text{ mm}/\text{BSA}^{0.5}$ , respectively;  $P < 0.05$ ). The presence of ETA was found to be associated with coarctation ( $P < 0.05$ ). In flow assessments, the peak pressure gradient was around 24–25 mmHg in the related area in two patients with coarctation compared to 12 mmHg in one patient.

Bovine-type aortic arch variation was found at a rate of 10.6%.

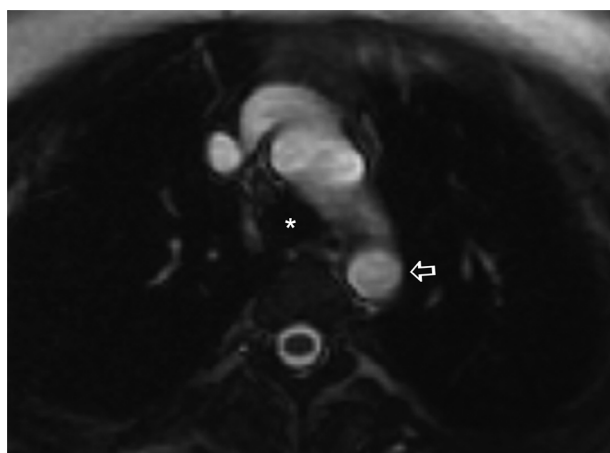
#### 3.3. Venous abnormalities

Partial anomalous pulmonary venous connections (PAPVCs) were found in 21.7% of the patients. Of these, six were in the form of a vertical vein, where some of the upper left pulmonary vein branches were flowing into the left brachiocephalic vein. Furthermore, abnormal venous connections associated with right pulmonary veins were identified in three patients. Both the vertical veins on the left and abnormal venous connections associated with the right pulmonary veins were observed in one patient (Figure 2). PAPVCs were observed at a higher rate in patients with the 45,X karyotype (8/24) compared to patients without the same (1/23 patients;  $P < 0.05$ ).

The occurrence of a persistent left superior vena cava (LSVC) was 8.7%. The mean ascending aorta and aortic root diameters were higher in the patients with LSVC ( $27.20 \pm 7.64 \text{ mm}/\text{BSA}^{0.5}$ ,  $26.73 \pm 5.77 \text{ mm}/\text{BSA}^{0.5}$ , respectively) compared to patients without ( $19.99 \pm 2.94 \text{ mm}/\text{BSA}^{0.5}$ ,  $21.54 \pm 2.23 \text{ mm}/\text{BSA}^{0.5}$ , respectively;  $P < 0.05$ ).

**Table 2.** Characteristics of patients.

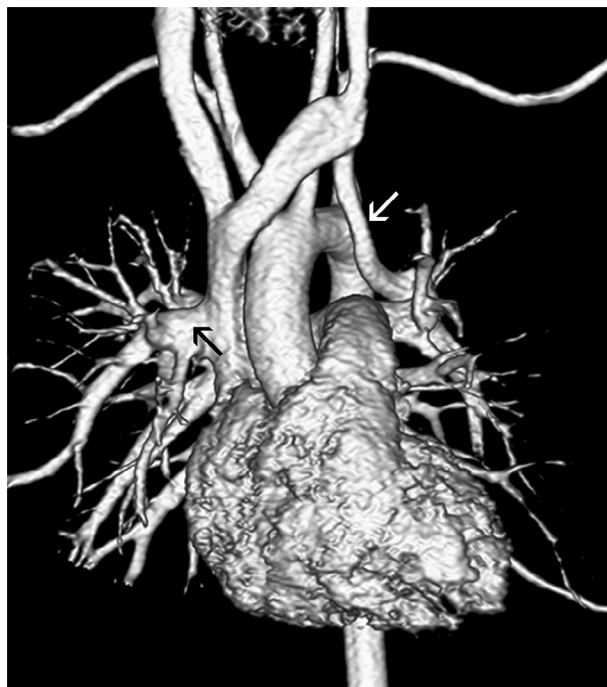
Total subjects (n)	47
Age (years, range & mean $\pm$ standard deviation)	7–22 (14.3 $\pm$ 3.5)
BSA, (m <sup>2</sup> , mean $\pm$ standard deviation)	1.18 $\pm$ 0.2
Subjects with 45,X karyotype (n & percent)	24 (51%)
Subjects with other karyotypes (mosaics, isochromosomes) (n & percent)	23 (49%)
Subjects with history of GH therapy (n & percent)	39 (83%)
Duration of GH therapy (months, range & mean $\pm$ standard deviation)	5–84 (36.5 $\pm$ 19.9)
Subjects still receiving GH (n & percent)	25 (53.2%)
Subjects with history of estrogen therapy (n & percent)	26 (55.3%)
Duration of estrogen therapy (months, range & mean $\pm$ standard deviation)	1–86 (22.1 $\pm$ 21.4)
Subjects with history of combined estrogen and progesterone therapy (n & percent)	13 (27.7%)
Duration of combined estrogen and progesterone therapy (months, range & mean $\pm$ standard deviation)	1–60 (24.6 $\pm$ 15.1)
Subjects with webbed neck (n & percent)	19 (40.4%)
Subjects with lymphedema (n & percent)	13 (27.7%)



**Figure 1.** ETA in a 15-year-old girl with TS. a) 3D volume rendering image shows flattening of the aortic arch (white arrow) and convex kinking along the lesser curvature (black arrow) b) Axial b-SSFP image reveals posterior origin of the left subclavian artery (open arrow) behind the trachea (asterisk).

### 3.4 Aortic valve

The aortic valve was bicuspid in 19.6% of the patients. The mean diameters of the descending and ascending aorta and mean Z-score for the ascending aorta were significantly



**Figure 2.** Bilateral PAPVCs in a 16-year-old girl with TS. 3D volume rendering image shows a vertical vein draining in to the left brachiocephalic vein (white arrow). In addition, right upper and middle lobe veins are draining into the superior vena cava (black arrow).

higher in patients with bicuspid aortic valve (BAV;  $16.27 \pm 2.62$  mm/BSA<sup>0.5</sup>,  $23.36 \pm 5.17$  mm/BSA<sup>0.5</sup>,  $3.01 \pm 2.56$ , respectively) compared to those with tricuspid aortic valve ( $14.77 \pm 1.44$  mm/BSA<sup>0.5</sup>,  $19.95 \pm 3.42$  mm/BSA<sup>0.5</sup>,  $1.31 \pm 1.89$ , respectively;  $P < 0.05$ ). Mean aortic valve area was significantly lower in patients with BAV ( $147.95 \pm 45.29$  mm<sup>2</sup>/BSA) compared to those without the same ( $176.42 \pm 26.78$  mm<sup>2</sup>/BSA;  $P < 0.05$ ). The presence of BAV was found to be associated with aortic regurgitation ( $P < 0.05$ ). The difference in the ascending aorta diameters measured in the first and second MRI assessments of patients with BAV was significantly higher compared to the group with tricuspid aortic valve ( $74$  mm/BSA<sup>0.5</sup> vs.  $-0.50$  mm/BSA<sup>0.5</sup> and  $0.04$  mm/month/BSA<sup>0.5</sup> vs.  $-0.03$  mm/month/BSA<sup>0.5</sup>, respectively). No association was found between the presence of BAV and ETA ( $P > 0.05$ ).

Aortic regurgitation was identified in eight (17%) patients. The mean diameter of the aortic root and ascending aorta and the Z-scores were higher in the patients with aortic regurgitation ( $24.13 \pm 5.43$  mm/BSA<sup>0.5</sup>,  $25.56 \pm 5.63$  mm/BSA<sup>0.5</sup>,  $4.34 \pm 2.91$ , respectively) compared to those without the same ( $21.43 \pm 2.11$  mm/BSA<sup>0.5</sup>,  $19.58 \pm 2.66$  mm/BSA<sup>0.5</sup>,  $1.08 \pm 1.40$ , respectively;  $P < 0.05$ ). Aortic regurgitation had an association with indices indicating the dilatation of an ascending aorta (Z-scores of  $>2$  for ascending aorta, ASI

>2 cm/m<sup>2</sup>, AD/DD >1.5), and the presence of LSVC and webbed neck ( $P < 0.05$ ).

### 3.5. Aortic diameter

The Z-score of the ascending aorta in 28.3% of the patients and the Z-score of the descending aorta in 15.2% of the patients were >2 (indicating dilatation of the aorta). Among the indices used for the dilatation of aortic diameter, ASI >2 cm/m<sup>2</sup>, which reflects dilatation of the ascending aorta, was detected in 28.3% of the patients and ASI >2.5 cm/m<sup>2</sup>, which is considered as a high risk for dissection, was observed in four (8.7%) patients. AD/DD >1.5, another index suggesting dilatation of the ascending aorta, showed 21.7% occurrence. The dilatation of the descending aorta, determined by a Z-score of >2, was observed in 15.2% instances. The coexistence of ascending and descending aortic dilatation was 6.5%. A Z-score for aortic sinus of >2, which indicates dilatation of the aortic root, was seen in 10.9% patients.

Z-scores of >2 for the descending and ascending aorta and the aortic root were correlated with the presence of BAV, whereas a Z-score of >2 for the descending aorta was correlated with the presence of ETA ( $P < 0.05$ ). ASI of >2 cm/m<sup>2</sup> was correlated with the presence of ETA ( $P < 0.05$ ). ASI of >2.5 cm/m<sup>2</sup> was associated with BAV. The mean ascending aortic diameter, the Z-score for the ascending aorta, ASI, and aortic root width were all significantly higher in the patients with webbed neck ( $22.36 \pm 5.44$  mm/BSA<sup>0.5</sup>,  $2.55 \pm 2.83$ ,  $2.45 \pm 0.56$  cm/m<sup>2</sup>,  $23.38 \pm 3.41$  mm/BSA<sup>0.5</sup>, respectively) compared to those without the same ( $19.47 \pm 2.20$  mm/BSA<sup>0.5</sup>,  $1.04 \pm 1.26$ ,  $1.79 \pm 0.28$  cm/m<sup>2</sup>,  $20.79 \pm 2.42$  mm/BSA<sup>0.5</sup>, respectively;  $P < 0.05$ ).

## 4. Discussion

The elongation of the transverse aortic arch (ETA) was the most frequently reported cardiovascular abnormality observed in our study population. Similar to the study by Kim et al. (8), the present study included pediatric and young adult patients, and the prevalence of ETA (37%) was lower relative to other studies (47%–49%) conducted with older adult TS patients (4), suggesting that the findings become apparent with increasing age. Similar to previous studies, the presence of ETA was associated with coarctation; however, as opposed to previous studies (4,8,13,18), no association was found between the presence of ETA and the 45,X karyotype, the presence of neck webbing, the presence of the LSVC, BAV, or aortic dilatation. On the other hand, the late takeoff and flattening of the arch was significantly associated with the diameter and the Z-score of the ascending aorta. Convex kinking of the inferior aortic contour was associated with Z-scores for the descending aorta. The present study, which measured the aortic valve area, suggested that the presence of ETA is associated with smaller aortic valve area.

Coarctation is reported in TS patients at rates varying from 5% to 20% (4,8,9,19). Coarctation has classically sharp concavity in the outer wall of the aorta, whereas kinking occurs at the lesser curvature in ETA (14,20). MR angiography ensures the identification of coarctation and collateral vascularization; it also allows the measurement of aortic diameters at various levels, which is important for surgical aspects. Moreover, phase-contrast velocity-encoded cine MR imaging can present increased velocity and peak pressure gradients at these levels, demonstrating coarctation severity (12,21,22).

PAPVC is a common anomaly in TS patients and it was found at a higher rate (22%) in the current study relative to other studies (13%–18%) (4,8,14,23). A careful assessment of all pulmonary venous branches is important for MRI identification of PAPVCs, because in most of these cases the aberrant vein appears as a thin vertical vein. Our personal experience during daily practice is that PAPVCs are easily missed even with MR angiography if not specifically investigated by means of assessing the pulmonary venous branches individually over thin-slice source and MPR images. On the other hand, MR angiography can easily display the entire vascular tree and is evidently more advantageous than TTE, which provides assessments from limited windows. This is proved by the considerably higher incidence of PAPVCs in the studies using Gd-enhanced 3D MR angiography compared to others that did not use MR angiography (8,14,24). PAPVC was typically left-sided in TS patients, which is also different from that of non-TS patients, in whom it is typically right-sided. Furthermore, the anomalous venous return was typically isolated and was not associated with intracardiac defects such as sinus venosus atrial septal defect, as seen in non-TS subjects (14,24). Similar to some of the previous studies, PAPVCs were associated with the 45,X karyotype (4,14,23) in the present study, whereas no such association was demonstrated with neck webbing, contrary to some of the previous studies.

BAV is a common cardiovascular anomaly in TS patients and its incidence ranges widely from 1.5% to 39.2% in TTE and MRI assessments (4,25). In the present study, the aortic diameters and Z-scores of both the ascending and descending aorta were higher in the presence of BAV and the progression in the diameter of the ascending aorta was greater in BAV cases. These results suggest that patients with BAV are at greater risk for aortic dilatation and thereby secondary complications. In the study by Hahn et al., which included the ascending aorta and investigated the association of aortic dilation with bicuspid aortic valves (26), a high prevalence of aortic root dilatation was reported in patients with a bicuspid aortic valve that occurred irrespective of altered hemodynamics

or age. The authors indicated that these findings support the hypothesis that bicuspid aortic valve and aortic root dilation may reflect a common developmental defect. In the present study, the association of BAV with both descending and ascending aorta dilatation also supports this hypothesis. Ferencik et al., while investigating changes in the size of the ascending aorta and aortic valve function with time in patients with congenitally bicuspid aortic valves, reported the mean rate of diameter progression at various levels as 0.5–0.9 mm/year and concluded that that progression of aortic diameter dilatation occurs irrespective of baseline valve function in adult patients with BAV (27). Mortensen et al. (28) evaluated 80 TS patients via two MR angiography examinations and found that the presence of BAV is associated with the progression in diameter of the aortic sinus. In addition to the studies demonstrating an association of BAV with aortic dilatation (28–30) in TS patients, there are also some that do not demonstrate such an association (8). The present study differs from earlier ones by not demonstrating any association between the presence of BAV and ETA (4,29).

Reference values in the present study for the ascending and descending aorta and aortic root diameters were based on the study of Kaiser et al. (13). Indices with the diameter of the ascending aorta indexed by the diameter of the descending aorta or BSA were also included; however, these indices can only demonstrate dilation of the ascending aorta. Therefore, a calculation of standardized Z-scores is generally more valuable when deciding on aortic dilatation. In the present study, a Z-score of  $>2$  and ASI of  $>2$  cm/m<sup>2</sup> for the ascending aorta produced the same result with regard to determination of ascending aorta dilatation. The rate of ascending aorta dilatation that was found based on an AA/DA ratio of  $>1.5$  was lower compared to these methods (28.3% vs. 21.7%). Coexistence of ascending and descending aorta dilatation in 6.5% of cases account for this difference and presents the limitation of the AA/DA ratio to demonstrate ascending aorta dilatation correctly (29). Aortic dilatation reported in TS patients ranges widely (12.5%–50%) and this discrepancy may result from differences in methodology, as well as the important issue of defining dilation (9,10,29). Studies on TS patients

reported that BAV, aortic coarctation, ETA, and karyotype 45,X are associated with larger baseline aortic diameters (28). In the present study, BAV, ETA and its components, webbed neck, and LSVC were associated with larger aortic diameters. In the study of Kim et al. (8), which was conducted with a similar age-range patient group to ours and used the same assessment method for Z-scores, aortic sinus dilatation had a high incidence rate of 30%; contrary to their findings, in the present study, the aortic sinus dilatation was less than the rate of ascending and descending aorta dilatations. Moreover, in contrast to their study, no correlation was found between aortic root dilatation and the presence of ETA.

GH therapy is widely used in TS patients to augment adult height. In the current study, most of the patients had a history of receiving GH and half of them were still receiving therapy during assessments. It was remarkable that ETA findings were observed at a lower rate in patients receiving GH therapy. As far as we know, although there is not another study evaluating the relation between GH therapy and ETA, Berg et al. (31) stated that GH therapy has a positive effect on aortic biophysical properties such as aortic wall distensibility. The present study employed BSA-corrected data and did not demonstrate any association between a history of using GH and aortic diameters; this was consistent with the results of Bony et al. (32).

The main limitations of the present study were the relatively small number of cases and absence of a normal control group of similar age. Calculating Z-scores based on the data of a single study (13) was another limitation. Further studies are needed to validate the normal ranges of aortic diameter in the pediatric population.

In summary, the most common anomaly, ETA, was observed to a lower degree in patients who were receiving GH therapy. Abnormal pulmonary venous returns are common in TS patients and were observed more frequently in the present study compared to rates reported in the literature. The presence of BAV is an important risk factor for aortic dilatation and its secondary complications, and aortic dilatation per unit time is greater in patients with BAV.

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