Major Vascular Anomalies in Turner Syndrome
Prevalence and Magnetic Resonance Angiographic Features

Vincent B. Ho, MD; Vladimir K. Bakalov, MD; Margaret Cooley, BA; Phillip L. Van, MS; Maureen N. Hood, MS, RN; Thomas R. Burklow, MD; Carolyn A. Bondy, MD

Background—Turner syndrome (TS) is associated with aortic coarctation and dissection; hence, echocardiographic evaluation of all patients is currently recommended. X-ray angiography in clinically symptomatic patients has suggested a range of other vascular anomalies, but the true prevalence of such lesions in TS is unknown. To better understand the prevalence and pathogenesis of cardiovascular defects in TS, we prospectively evaluated a group of asymptomatic adult volunteers with TS using magnetic resonance (MR) angiography.

Methods and Results—A total of 85 adults with TS and 27 normal female adult volunteers underwent gadolinium-enhanced 3D MR angiography. A high prevalence of aortic anomalies was seen in women with TS, including elongation of the transverse arch (49%), aortic coarctation (12%), and aberrant right subclavian artery (8%). Venous anomalies were also prominent, including persistent left superior vena cava (13%) and partial anomalous pulmonary venous return (13%). None of these anomalies were found in healthy female controls. The constellation of elongation of the transverse arch, aortic coarctation, and persistent left superior vena cava was significantly associated with women with TS. Neck webbing and increased thoracic anterior-to-posterior dimension diameters were strong predictors for arterial and venous anomalies.

Conclusions—Thoracic vascular anomalies are common in TS, occurring in ≈50% of a group not preselected for cardiovascular disease. The highly significant association between neck webbing, increased chest diameter, and these vascular anomalies suggests that in utero, centrally localized lymphatic obstruction may contribute to these cardiovascular deformities in TS. Improved recognition of these often-undetected vascular lesions may be important for identification of patients in need of closer cardiovascular monitoring. (Circulation. 2004;110:1694-1700.)

Key Words: Turner syndrome ■ angiography ■ magnetic resonance imaging ■ aorta ■ veins

Originally described in 1938 by Henry Turner,1 Turner syndrome (TS), or monosomy X, results from complete or partial monosomy for the X chromosome. This is a relatively common chromosomal disorder, affecting ≈1 in 2500 live female births. The most common features are short stature and gonadal dysgenesis, but the most serious clinical aspect of the syndrome is due to congenital cardiovascular anomalies that include, most critically, aortic coarctation and dissection.2–7 Over the years, the reported incidence of cardiovascular lesions has varied from 23%8 to as high as 45%.2 Variations in incidence are attributable to variations in noninvasive methods used for screening and the types of lesions that they can characterize. Using echocardiography and black-blood T1-weighted spin-echo MRI in a group not selected for cardiovascular disease, Dawson-Falk et al12 reported a 45% prevalence of cardiovascular lesions, with bicuspid aortic valve (17.5%), aortic coarctation (12.5%), and persistent left superior vena cava (LSVC; 5%) representing some of the more common lesions. However, TS has also been associated with other arterial and venous anomalies, notably anomalous pulmonary venous return4,8–13 and pseudocoarctation of the aorta.14–17

A more comprehensive angiographic characterization of the variety and incidence of arterial and venous structural anomalies of TS, however, has yet to be described. This is understandable given the relative risks associated with conventional catheter angiography, which has precluded its use for routine screening in asymptomatic patients with TS. However, recent improvements in magnetic resonance angiography (MRA), namely, the development of gadolinium (Gd)-enhanced 3D MRA technique,18–21 have enabled the reliable depiction of arterial and venous anatomy without the inherent risks and clinical concerns of catheter x-ray angiography. On most current magnetic resonance (MR) scanners, Gd-enhanced 3D MRA can be performed within a single

Received January 23, 2004; de novo received April 19, 2004; accepted June 22, 2004.
From the Departments of Radiology and Radiological Sciences (V.B.H., M.N.H.) and Pediatrics (T.R.B.), Uniformed Services University of the Health Sciences, Bethesda, Md; Diagnostic Radiology Department (V.B.H., M.N.H.), Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Md; and Developmental Endocrinology Branch (V.K.B., M.C., P.L.V., C.A.B.), National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md.
The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of Defense or the Uniformed Services University of the Health Sciences.
Correspondence to Vincent B. Ho, MD, Department of Radiology and Radiological Sciences, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814. E-mail vho@usuhs.mil or vho@nih.gov
© 2004 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000142290.35842.B0
breath hold and can provide high spatial resolution angiographic delineation that rivals that of conventional x-ray angiography but without the concerns of radiation exposure, catheter placement, contrast media anaphylaxis, or nephrotoxicity. In the present study, we evaluated the spectrum, prevalence, and associations of thoracic arterial and venous anomalies in a group of adults with TS, not selected for cardiovascular disease, and investigated their association with a variety of clinical parameters.

Methods

Eighty-five adult patients (average age 37±11 years) with karyotypically proven TS and 27 healthy female subjects (aged 36±10 years) provided written informed consent for voluntary participation in this study protocol approved by the National Institute of Child Health and Human Development (NICHD) Institutional Review Board. Study participants were largely self-referred, having learned about the study through the NICHD and TS World Wide Web-site notices. We did not recruit subjects through medical specialists.

Imaging was performed on a 1.5-T MR scanner (Signa, General Electric Medical Systems) with a phased-array coil and included axial and coronal T1-weighted fast spin echo and oblique sagittal fast gradient echo pulse sequences. Gd-enhanced 3D MRA was performed with a fast sagittal or oblique sagittal 3D spoiled gradient echo pulse sequence (repetition time, 6.2 to 7.3 ms; echo time, 1.2 to 2.2 ms; flip angle, 20° to 30°; partition thickness, 2.0 to 2.6 mm; number of acquisitions, 1; field of view, 28 to 35 cm; acquisition matrix, 256×128 to 256; acquisition time, 20 to 29 seconds) and a 0.2-mmol/kg dose of Gd-chelate contrast media administered via an antecubital vein with an MR-compatible injector (Spectris, Medrad). Zero filling (ZIP 512, General Electric Medical Systems) was implemented when available. Timing of the initial “arterial-phase” Gd-enhanced 3D MRA was achieved with an automated bolus detection scheme (MR SMARTPREP, General Electric Medical Systems) with the monitoring volume placed within the aortic arch. Postcontrast delayed phase imaging included axial fat-suppressed spoiled gradient echo images (repetition time, 150 ms; echo time, 1.3 to 1.4 ms; flip angle, 75°; slice thickness, 7 to 10 mm; number of acquisitions, 1; field of view 28 to 39 cm; acquisition matrix, 256×192).

In 6 patients with partial anomalous pulmonary venous return (PAPVR), oblique axial cine phase-contrast imaging (velocity encoding, 200 cm/s; direction, through-plane; repetition time, 33 ms; echo time, 6.2 or 6.3 ms; flip angle, 20°; slice thickness, 7 mm; matrix, 256×128; field of view, 25 to 35 cm) was performed through the base of the heart. Blood flow though the aortic root (systemic flow or Qs) and the pulmonary artery (pulmonary flow or Qp) was measured from phase-contrast phase map images with flow analysis software (Cine Tool, General Electric Medical Systems) on an independent computer workstation.

Evaluation of the MR images was performed blinded to each subject’s clinical presentation and past cardiovascular history. Images were evaluated for the presence of arterial and venous anomaly. In each subject, the maximum superior-to-inferior dimension (SI), maximum anterior-to-posterior dimension (AP) and maximum right-to-left dimension (RL) of the thoracic cavity were measured from T1-weighted fast spin echo images. Body surface area (BSA) was calculated with the equation:

\[ \text{BSA} = \frac{\text{height} \times \text{weight}}{3600} \]

Continuous data are expressed as mean with SD. Nominal data are expressed as numbers and percent. Comparison between group means was made by 1-way ANOVA with Fisher’s protected least significant difference, after log transformation of data that were not normally distributed. Associations were tested by \( \chi^2 \) and Fisher’s exact test. Contribution of multiple variables in explaining the presence of a particular anomaly was tested by multiple forward stepwise regression in a linear model. Statistical significance was accepted if the probability value was <0.05. Analysis was performed with standard statistical software (SigmaStat, version 2.0, SPSS Inc).

Results

Subject Characteristics

Study subject characteristics are summarized in Table 1. The 2 groups were similar in age, but as expected, women with TS were shorter (\( P<0.0001 \)) and had smaller mean BSA (P=0.008). Thoracic cavity dimensions were determined to investigate whether reduced chest size could contribute to...
developmental anomalies of the great vessels. As expected, thoracic width and height were reduced in TS (Table 1), but when corrected for BSA, the width was actually relatively increased in TS (270±29 versus 241±14 mm, P<0.05), and the height was not different from controls. In contrast, thoracic AP diameter was significantly greater in women with TS, even without correction for body size (Table 1). Thoracic volume was not significantly smaller in TS when corrected for BSA (data not shown).

Arterial Anomalies

The aortic arch was noted to course normally to the left in all subjects. No subjects were noted to have an aortic dissection or aneurysm (aortic diameter ≥5 cm). The vascular anomalies detected in women with TS and controls are summarized in Table 2. In women with TS, the most common arterial finding was elongation of the transverse arch (ETA; 42/85, 49%), which was typically seen as increased distance between the origins of the left common carotid and the left subclavian arteries, with flattening of the arch and kinking along its lesser curvature (Figure 1), a feature sometimes referred also as “pseudocoarctation.”

ETA was defined by the presence of both (1) posterior origin of the left subclavian artery behind the trachea on axial images and (2) inward indentation or convex kinking of the inferior aortic contour along the lesser curvature. Coarctation of the aorta was the second most common arterial finding, detected in 10 subjects (12%). Coarctation (Figure 2) was defined by the presence of both (1) concentric narrowing of the aorta (typically juxtaductal in location) and (2) a posterior “shelf” along the distal cephalic aortic contour.

Four women with TS with coarctation identified on MRA had a prior history of coarctation repair. In the remaining 6 subjects, the coarctation detected on MRA was clinically undetected or silent. None of the subjects with coarctation had dilated collaterals on Gd-enhanced 3D MRA or evidence of a flow jet on fast gradient echo pulse sequences to suggest
TABLE 3. Blood Pressure vs Aortic Abnormality in Women With TS

<table>
<thead>
<tr>
<th></th>
<th>Normal Vessels (n=35)</th>
<th>Isolated ETA (n=21)</th>
<th>All ETA (n=42)</th>
<th>Coarctation (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>114±11</td>
<td>123±13*</td>
<td>119±12</td>
<td>117±11</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>70±9</td>
<td>75±7*</td>
<td>75±8*</td>
<td>77±7*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>84±9</td>
<td>91±8*</td>
<td>90±8*</td>
<td>90±8*</td>
</tr>
<tr>
<td>PP (mm Hg)</td>
<td>43±7</td>
<td>47±12</td>
<td>44±10</td>
<td>40±7</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; and PP, pulse pressure.

Values are mm Hg.

*P<0.05 compared with subjects with normal vessels using ANCOVA with age as a covariate.

Discussion

This is the first MRA study to evaluate the anatomy of thoracic great vessels in TS. This angiographic study has demonstrated a high prevalence of unsuspected structural abnormalities of the thoracic vessels in women with TS. Most prominently, we found that roughly half had marked structural deviations of the aortic arch, described here as ETA, and 7% had an unsuspected coarctation of the aorta. This is in line with clinical features referable to significant left-to-right shunting.

Associations

The presence of coarctation was always associated with ETA (Table 3). In addition, the presence of an LSVC was significantly associated with ETA (P=0.003) and with an aberrant right subclavian artery (P=0.01). ETA was an isolated anomaly in ∼50% of subjects with this finding, as was PAPVR (Table 3). In contrast, a persistent LSVC and aberrant right subclavian artery were always associated with other anomalies.

The presence of neck webbing was significantly associated with coarctation, ETA, PAPVR, and LSVC (P<0.05; Table 4). Comparison of thoracic measurements (SI, AP, RL, and thoracic volume) demonstrated a significant association only between AP diameter and ETA (χ² 7.1, P=0.008). Of the group with TS, 54 of 85 had a karyotype 45X (fewer than 10% of other cell lines on a 50-cell peripheral karyotype). This karyotype was significantly associated with ETA, coarctation, LSVC, and PAPVR (P<0.05). The contributions of age, BSA, thoracic cage diameters, karyotype, and neck webbing to the likelihood of finding ETA were analyzed by forward stepwise regression analysis in a linear model. Only 2 variables, neck webbing (P=0.036) and AP thoracic diameter (P=0.002), were significantly associated with ETA. Similar analyses for the other major vessel anomalies were limited because of small numbers and underspecified models.
with an earlier MR study reporting 3 of 40 such “silent” lesions. Coarctation was always found in the context of ETA, which suggests that similar pathogenetic processes contribute to these anomalies. Although this association of aortic anomalies might have been expected, we also found a significant association between the presence of ETA and the persistence of an LSVC, for which the pathogenetic connection is not so obvious. We do not think that the extraordinarily high prevalence of vascular anomalies found in the present study is due to a bias toward more severely affected patients in our study population. Our subjects were largely self-referred, and most traveled a fair distance to the Washington, DC metropolitan area to participate, so if any bias affected our recruitment, it was likely toward healthier, more functional people. Few study subjects were followed up by cardiologists, and ∼30% had never before had any cardiac imaging.

A leading hypothesis concerning the origin of congenital cardiovascular malformations in TS posits a relation to the lymphatic hypoplasia/obstruction that affects a large proportion of 45X fetuses. Clark25 initially suggested that jugular lymphatic obstruction in utero resulted in dilated lymphatic vessels around the aortic root that, as a matter of speculation, might compress developing outflow structures, resulting in a range of aortic deformations. This theory further proposes that aortic root compression results in decreased blood flow across the transverse arch and isthmus and thus contributes to aortic arch hypoplasia and coarctation. However, there is no direct evidence for compression of the aortic root in TS, and additional studies have found a hypoplastic left heart in a

| TABLE 4. Prevalence, Combinations, and Associations of Major Vessel Abnormalities in TS |
|---------------------------------------------|-------------------------------|-------------------------------|-------------------------------|
|                                             | Prevalence of TS (n=85)     | Web Neck (n=36)              | 45X (n=54)                  |
| Aorta                                       |                              |                              |                             |
| ETA                                         | 42 (49%)                     | 4.3; P=0.039 4.7; P=0.030    | Isolated 21/42              |
|                                             |                              | With coarctation 10/42*      |                              |
|                                             |                              | With aberrant RSCA 4/42      |                              |
|                                             |                              | With LSVC 10/42*             |                              |
|                                             |                              | With PAPVR 6/42              |                              |
|                                             | Coarctation 10 (12%)         | 4.9; P=0.026 4.8; P=0.028    | Isolated 0/10               |
|                                             |                              | With ETA 10/10*              |                              |
|                                             |                              | With aberrant RSCA 1/10      |                              |
|                                             |                              | With LSVC 3/10               |                              |
|                                             |                              | With PAPVR 1/10              |                              |
|                                             |                              | With >2 4/10                 |                              |
| Aberrant RSCA                                | 7 (8%)                       | 1.5; P=0.220 0.7; P=0.388    | Isolated 0/7                |
|                                             |                              | With ETA 4/7                 |                              |
|                                             |                              | With coarctation 1/7         |                              |
|                                             |                              | With LSVC 3/7*               |                              |
|                                             |                              | With PAPVR 2/7               |                              |
|                                             |                              | With >2 3/7                  |                              |
| Major veins                                  |                              |                              |                             |
| Left SVC                                    | 11 (13%)                     | 3.4; P=0.063 5.6; P=0.018    | Isolated 0/11               |
|                                             |                              | With ETA 10/11*              |                              |
|                                             |                              | With coarctation 1/11        |                              |
|                                             |                              | With aberrant RSCA 3/11*     |                              |
|                                             |                              | With PAPVR 1/11              |                              |
|                                             |                              | With >2 4/11                 |                              |
| PAPVR                                       | 11 (13%)                     | 6.3; P=0.012 5.6; P=0.018    | Isolated 5/11               |
|                                             |                              | With ETA 4/11                |                              |
|                                             |                              | With coarctation 1/11        |                              |
|                                             |                              | With aberrant RSCA 2/11      |                              |
|                                             |                              | With LSVC 1/11               |                              |
|                                             |                              | With >2 1/11                 |                              |

RSCA indicates right subclavian artery; SVC, superior vena cava.

*Statistically significant (P<0.05) association by Fisher exact test.
number of 45X fetuses, which suggests that the defect lies further upstream.26

Shinebourne and Elseed27 theorized that coarctation results from altered flow patterns due to a left-sided blockage within the fetal circulation, which in turn results in elevated pulmonary and ductus arteriosus blood flow. Abnormal flow via the ductus to the isthmic portion of the arch is predicted to produce hypoplasia, tortuosity, and/or coarctation of the aorta in the juxtaductal region. The reduction of left heart blood flow suggested by this theory could explain the left heart hypoplasia noted above. The present study adds important new elements to this discussion on the origin of congenital cardiovascular defects in TS. We have shown that a persistent LSVC is linked to aortic anomalies in TS and that neck webbing, the postnatal residua of fetal lymphedema, is significantly associated not only with ETA and coarctation but also with the venous anomalies LSVC and PAPVR. Thus, the present study shows that the pathogenetic process leading to cardiovascular malformation in TS involves both the major inflow and outflow tracts of the heart and occurs most often in fetuses with lymphedema. A possible explanation for the statistically significant association between left- and rightsided cardiovascular defects noted in the present study could be that obstruction to forward flow caused by lymphatic compression of the developing left ventricle/aortic root results in back pressure or congestion in the fetal inflow structures, resulting in persistent anomalies of major thoracic venous structures. Many TS patients are reported to have a “shield-like” chest.3 We investigated the possibility that a disproportion between thoracic cage and great vessel development might explain some of the observed vascular anomalies. Interestingly, and contrary to our expectations, we found that chest AP diameter is increased in women with thoracic vascular anomalies (ETA). It appears possible that an increased AP dimension may reflect the presence of an intrathoracic lymphocele during fetal development, representing another potential linkage between fetal lymphedema and congenital cardiovascular defects.

Aortic arch malformations such as ETA and coarctation in a region subject to high-flow velocity and shear stress may cause alterations in flow patterns that could have clinical consequences. It is interesting that systolic and diastolic blood pressures were significantly higher in women with ETA. The significance of this is unknown but is intriguing. There are many potential causes of hypertension in women with TS: endothelial, neurohormonal, and coarctation of the aorta. It is recognized that the elastic wall properties of the aorta in coarctation are abnormal28–31; alterations in vascular wall compliance itself can lead to hypertension. It is possible that changes in vascular wall compliance may accompany the anatomic aberrations in the aorta and its arch vessels, leading to the findings of elevated blood pressure, even in the absence of a clinically significant aortic coarctation. Further evaluation using dynamic measurement of blood flow across the transverse arch may prove insightful as to the true significance of this finding. It is also notable that the patients with previously undiagnosed coarctation of the aorta, albeit only 6 subjects, also were noted to have elevated diastolic blood pressures.

One of the greatest concerns in TS is the risk of aortic dissection, which affects 1% to 2% of this population.32,33 There has never been a prospective study of risk factors for aortic dissection in TS, but retrospective analyses32,33 suggest that hypertension, coarctation, and bicuspid aortic valve are risk factors in TS, as in nonsyndromic aortic dissection. However, ≈10% of cases do not have any apparent risk factors, and it thus appears possible that clinically silent anomalies such as ETA and coarctation, as documented in the present study, could predispose to aortic dissection in TS. The anatomic distribution of reported dissections (ie, aortic root, ascending aorta, transverse arch, and descending aorta35) suggests that the entire thoracic aorta is at risk. Improved recognition of aortic structural anomalies in patients with TS may provide additional insight for surveillance guidelines in TS. Further studies, including the evaluation of blood flow patterns across the transverse arch and tracking the evolution of arch morphology, blood flow patterns, and systemic blood pressure over time, are required to more accurately assess the clinical significance of these novel findings.

Previous reports have rarely noted venous abnormalities in TS. Dawson-Falk et al2 report 2 of 40 subjects with a persistent LSVC, and Prandstraller et al34 reported <3% prevalence for PAPVR. In the present series, both venous anomalies were rather more common, with each occurring in roughly 13% of patients. The apparent higher incidence of these venous abnormalities in the present study may be attributed to the improved ability to detect venous anatomy using Gd-enhanced 3D MRA,21 especially for identification of PAPVR, which may be subtle on other forms of imaging. As in other reported cases,10–13,35 the finding of 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.36 Moreover, PAPVR was typically left-sided (ie, anomalous left pulmonary vein) in patients with TS, which also differs from that of non-TS patients, in whom it is typically right-sided.36 Patients in the present study with TS and PAPVR presented clinically in a very similar manner to those reported previously10–13,35 in that their left-to-right shunt (average Qp/Qs 1.1) was not large and their lesions were otherwise not evident clinically. PAPVR, however, has been reported to occasionally appear with more dramatic consequences if the left-to-right shunt is large. Price and Willey37 reported 2 adult patients (ages 35 and 47 years) with TS (from a series of 135 patients with TS) who presented with congestive heart failure secondary to significant left-to-right shunting by large PAPVR lesions.

The present study shows that Gd-enhanced 3D MRA can provide meaningful angiographic depiction of arterial and venous anomalies that may have important clinical implications for the management of patients with TS. Current guidelines for management of patients with TS recommend echocardiographic imaging with possible MR assessment in patients with suspicion of cardiovascular manifestation.38 Given the high prevalence of unanticipated aortic and venous anomalies in the present study population, attention for these anomalies is advised. Although many of the lesions described
may be identified with traditional black-blood spin echo and bright-blood gradient echo pulse sequences, the performance of contrast-enhanced MRA might be beneficial, especially in problematic cases.

References

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Circulation. 2004;110:1694-1700; originally published online September 7, 2004; doi: 10.1161/01.CIR.0000142290.35842.B0
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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