

Moderate Aortic Enlargement and Bicuspid Aortic Valve Are Associated With Aortic Dissection in Turner Syndrome: Report of the International Turner Syndrome Aortic Dissection Registry

Misty Carlson, Nathan Airhart, Leo Lopez and Michael Silberbach

Circulation. 2012;126:2220-2226; originally published online October 2, 2012;
doi: 10.1161/CIRCULATIONAHA.111.088633

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circ.ahajournals.org/content/126/18/2220>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>

Moderate Aortic Enlargement and Bicuspid Aortic Valve Are Associated With Aortic Dissection in Turner Syndrome Report of the International Turner Syndrome Aortic Dissection Registry

Misty Carlson, MD; Nathan Airhart, MD; Leo Lopez, MD; Michael Silberbach, MD

Background—Girls and women with Turner syndrome are at risk for aortic dissection and rupture. However, the size of the aorta and the clinical characteristics among those with Turner syndrome and dissection have received little attention.

Methods and Results—We obtained medical records from 20 individuals who voluntarily participated in the International Turner Syndrome Aortic Dissection Registry. Type A dissections occurred in 17 of 20 (85%) cases, and type B occurred in 3 cases of which 1 occurred after coarctation stent placement. Of those with spontaneous aortic dissections, 18 of 19 (95%) had an associated cardiac malformation that included a bicuspid aortic valve. In 1 individual there was no predisposing finding other than the presence of Turner syndrome. Associated pregnancy was documented in 1 of 19 (5%). More than half (13/19, 68%) came to medical attention >24 hours after the onset of symptoms. For those with type A dissections, the mean ascending aortic size index was 2.7 ± 0.6 cm/m² (n=9).

Conclusions—Aortic dissection in Turner syndrome occurs in young individuals at smaller aortic diameters than in the general population or other forms of genetically triggered aortopathy. The absence of aortic valve or other cardiac malformations appears to markedly reduce the risk of aortic dissection. However, aortic dissection can occur in Turner syndrome without cardiac malformations or hypertension. Individuals with Turner syndrome who are >18 years of age with an ascending aortic size index >2.5 cm/m² should be considered for an aortic operation to prevent aortic dissection. (*Circulation*. 2012;126:2220-2226.)

Key Words: aneurysm ■ aorta ■ Turner syndrome

Aortic dissection occurs in individuals with fibrillin-1 mutations (Marfan syndrome), collagen mutations (Ehlers-Danlos syndrome), transforming growth factor β -receptor mutations (Loeys-Dietz syndrome), and postulated primary disorders of aortic wall composition such as familial thoracic aortic disease and dissection, bicuspid aortic valve (BAV), and Turner syndrome (TS).¹ Despite the fact that aortic dissection occurs rarely in TS (36/100 000 person years), it is 6 times more common in the TS population than in the general population.² It also occurs at a much younger age in the TS population than in the general population. The average age at dissection in the TS population is 30.7¹ years in comparison with 68 years³ in the general female population. To better understand the natural history, risk factors, and echocardiographic features of aortic dissection in women with TS, the International Turner Syndrome Aortic Dissection (ITSAD) Registry was established in 2005. This review of the registry data describes the signs, symptoms, and echocardiographic features preceding aortic dissection in 20 women with TS.

Clinical Perspective on p 2226

Methods

Study Population

A voluntary registry was established to capture cases of aortic dissection in women with TS. Subjects were recruited through the Turner Syndrome Society of the United States (TSSUS; <http://www.turnersyndrome.org/>) and by word of mouth from 2005 to 2010. Survivors themselves, or individuals aware of a TS dissection, were either mailed a questionnaire or completed it directly on the TSSUS Web site. The questionnaire was used to screen subjects so that all those enrolled in the registry had both TS and an aortic dissection. Enrollees were asked to sign medical release forms that were then sent to the primary care provider, primary cardiologist, and any medical center or medical care provider who administered care during the dissection event. No subjects had a genetic abnormality other than TS. Written consent was obtained from all subjects or their parents or guardians, and a written assent was obtained from children able to read the form.

Received December 21, 2011; accepted September 7, 2012.

From the Oregon Health & Science University; Portland, OR (M.C., N.A.); and Children's Hospital at Montefiore, Bronx, NY (L.L., M.S.).

Correspondence to Michael Silberbach, MD, Department of Pediatrics, CDRC-P, Oregon Health and Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239. E-mail silberbm@ohsu.edu

© 2012 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.111.088633

Table 1. Dissection Registry Subjects

Patient No.	Age at Dissection, y	Cardiac Diagnosis (Comment)	Hypertension (Y/N)	Location of Dissection	Symptom Duration	Outcome
1 ¹	18	BAV	N	Type A	>24 hr	Death
2	18	BAV, coarctation	Y	Type A	>24 hr	Death
3	21	BAV	N	Type A	>24 hr	Alive
4	23	BAV, h/o IAA	N	Type A	>24 hr	Death
5	24	BAV, coarctation	N	Type A	>24 hr	Death
6	27	BAV	N	Type A	>24 hr	Alive
7	28	BAV	N	Type A	<24 hr	Alive
8	28	BAV	Y	Type A	>24 hr	Death
9	28	BAV, unrepaired coarctation	N	Type A	<24 hr	Death
10	29	BAV	Y	Type A	>24 hr	Death
11*	29	BAV	N	Type B	<24 hr	Death
12	30	BAV	Y	Type A	>24 hr	Death
13 ¹	34	BAV	N	Type A	<24 hr	Death
14	35	coarctation (dissection during stent)	Y	Type B	<24 hr	Alive
15	37	BAV, VSD	Y	Type A	>24 hr	Death
16	40	None	N	Type A	<24 hr	Death
17	41	BAV	N	Type A	>24 hr	Alive
18	44	BAV	N	Type A	>24 hr	Alive
19	48	BAV/severe AS	Unknown	Type A	<24 hr	Alive
20*	48	BAV, aberrant RSA	Y	Type B	>24 hr	Alive

Mean, SD, med, 1st quart, 3rd quart 30.5, 8.7, 28, 23.5, 38.5
(for type A dissections only)

*Not previously reported, reference is given for known prior reports others may or may not have been reported.

AS indicates aortic stenosis; BAV, bicuspid aortic valve; IAA, interrupted aortic arch; VSD, ventricular septal defect; RSA, right subclavian artery.

Questionnaire

Each subject with TS or her parent completed a standardized questionnaire regarding karyotype, 45,X or non-45,X (non-45,X includes a variety of other TS chromosomal arrangements), history of heart disease, previous cardiac surgery, hypertension, growth hormone therapy, other medications, thyroid disorders, renal or urologic defects, hearing defects, and other medical problems.

Data Collection

All available medical records were reviewed with particular attention paid to Turner genotype/phenotype, heart disease (from echocardiographic, magnetic resonance imaging, or autopsy evaluation), history of hypertension, blood pressures, age, symptoms, outcome, surgical and/or autopsy findings, tissue histology, dates of recent echocardiographic studies, and aortic root and ascending aortic size. In particular, we looked for evidence of serial measurements of the ascending aortic diameter to compute the aortic size index (ASI). ASI⁴ was computed by dividing the size of the aortic root or ascending aorta by the body surface area (BSA).⁵ All available echocardiogram reports were reviewed. The data from each report included the date of the echocardiogram, the patient's height, weight, and BSA, the diagnosis and characterization of congenital heart disease if present, and the size of the aortic root and ascending aorta if available. For the purposes of this study, sinus of Valsalva diameter was considered to be synonymous with the aortic root diameter. Also, the ascending aorta was assumed to represent the region above the sinotubular junction and proximal to the innominate as recently described.⁶ Study protocols were approved by the Institutional Review Board at Oregon Health & Science University.

Statistical Analysis

Descriptive analysis (mean and standard deviation for continuous variables, frequency and relative frequency for categorical variables)

was performed on each parameter of interest to study the distribution of the data. General linear mixed-model regression with repeated measures was used to examine changes over time of the ASI at the level of the ascending aorta.

Results

Aortic dissections occurred in 20 individuals between 1988 and 2010; the median year was 2004 (Tables 1 and 2). Seventeen of the 20 registry subjects had a Stanford type A aortic dissection,⁷ and 3 patients developed a type B dissection (cases 11, 14, and 20). In 1 subject (case 14), a type B dissection occurred in the cardiac catheterization laboratory during stent placement for coarctation of the aorta. Her data were not included in further comparisons. Thus, among the entire cohort of those with spontaneous aortic dissections only 2 of 19 (11%) had type B aortic dissection.

The average age at the time of dissection was 31.5 years \pm 9.1 (range, 18–48 years). Eighteen of the 19 subjects had congenital heart disease documented by echocardiography, surgery, or autopsy. One subject had no history of hypertension and had no evidence of congenital heart disease found during autopsy. All of the 18 subjects with congenital heart disease had a BAV. Five subjects had an aortic arch obstruction (3 with repaired coarctation, including 1 who was stented at the time of dissection, and a fourth who had been previously operated on for an interrupted aortic arch). The fifth subject had an unrepaired coarctation that was not discovered until autopsy (case 9). Eighteen of the 19 subjects

Table 2 Echocardiographic Measurements (cm)

Patient No.	Aortic Root (ASI)	Ascending Aorta (ASI)
1 ¹	2.6 (2)	3.2 (2.5)
2	—	—
3	4.3 (2.5)	—
4	3.2 (2.3)	4.1 (2.9)
5	—	3.6 (3)
6	4.5 (3)	5 (3.3)
7	—	—
8	2.7 (1.7)	4.2 (2.7)
9	3.6 (2.5)	4.5 (3.2)
10	2.2 (1.7)	—
11*	3.3 (2.1)	—
12	3.8 (2.5)	2.3 (1.5)
13 ¹	3.5 (2.2)	5.1 (3.2)
14	1.8 (1.1)	—
15	3.4 (2.2)	—
16	—	—
17	—	—
18	—	4.8 (2.9)
19	—	—
20*	3.1 (2)	3 (1.9)
Mean, SD, med, 1st quart, 3rd quart (type A dissections only)	2.3, 0.4, 2.3, 1.9, 2.5	4.1, 0.9, 4.2, 3.4, 4.9

ASI indicates aortic size index.

*Not previously reported, reference is given for known prior reports others may or may not have been reported.

had documentation of at least 1 blood pressure measurement. One third of these subjects (6/18, 33%) met criteria for hypertension based on blood pressure recordings that were documented in the medical records. Nine of the 19 (47%) subjects were being treated with antihypertensive medications at the time of the dissection. Ten of 19 (53%) subjects had taken growth hormone for short stature.

Symptoms and Survival in Patients With Spontaneous Dissection

All but 1 subject (1/19, 5%) had symptoms before death or operation (Tables 1 and 2). One subject (1/19, 5%) died 1 hour after the onset of chest pain. Five additional subjects (5/19, 26%) reported symptoms between 1 and 24 hours before presentation, but 13 subjects (13/19, 68%) had symptoms for >24 hours before presentation. The most common symptoms were chest pain as reported by 16 of 19 subjects, neck/back pain (6/19), shortness of breath/dyspnea (5/19), nausea/vomiting (5/19), weakness/dizziness (4/19), feeling of doom (2/19), and abdominal pain (1/19). The initial presentation was sudden death for 9 subjects (7/9 presented in cardiac arrest). Seven of the 19 (37%) survived after developing a dissection. The duration of symptoms did not correlate with the likelihood of survival (30% >24 hours versus 50% <24 hours, Fisher exact test $P=0.99$). However, when younger age is taken into account, it appears that death tends to be more likely in those with a longer duration of symp-

toms. The small sample size does not allow significance, but the trend appears to be that the younger TS subjects ignore symptoms longer and are more likely to die. For example, among the TS subjects who were younger than the median age of 31 years, 9 had symptoms >24 hours before presentation and 7 died (78%).

Pregnancy

Three registry subjects had a history of pregnancy before their aortic dissection (case 6, 11, and 20). In one instance (case 19), a successful pregnancy and delivery occurred 2 years after the aortic dissection. Of the 3 subjects who were pregnant before dissection, one underwent assisted reproductive therapy (case 11); in the other subjects (cases 6 and 20), the pregnancies occurred spontaneously in individuals with mosaic karyotypes. Two of these subjects had spontaneous type B dissections (cases 11 and 20). Interestingly, these were the only cases of spontaneous dissection that were type B in the entire cohort. Case 6 had an unobstructed BAV and a type A dissection. Her ascending aorta was found to be 3.3 cm/m², which was the largest echo diameter of an ascending aorta reported in this study. The echo study was performed 90 days before her dissection. Case 11 had a type B dissection in her third trimester. She also had a BAV, mild dilation of her ascending aorta, and a large aneurysm of the left subclavian artery documented by computed tomography scan and echocardiography 8 years before the pregnancy. She underwent assisted reproductive therapy with implantation of 2 embryos. Symptoms occurred at 36 weeks gestation, and maternal death followed an emergent cesarean delivery by which 2 healthy infants were delivered. Postmortem examination confirmed that the origin of the dissection was at the takeoff of the aneurysmal left subclavian artery. In case 20, there was a history of a spontaneous pregnancy 17 years before the event. A computed tomography scan identified a left aortic arch and indicated that the origin of the dissection was at the origin of an anomalous right subclavian artery.

Echocardiography

Fifteen of the 19 registry subjects who had spontaneous dissections had imaging reports with aortic dimensions available for review. Of those with preceding echocardiograms, 7 of the 15 subjects had serial measurements: 5 had serial measurements of the ascending aorta (mean=2.2 measurements; range, 1–5; mean total follow-up time, 733 days). Two subjects had serial measurements of the aortic root.

Among the 9 individuals with type A aortic dissection and available echocardiographic data, the range of ascending aortic diameter was 2.3 to 5.1 cm (mean=4.1±0.9 cm). The minimum aortic size index-ascending aorta (ASI-AAO) was 1.5 cm/m², and maximal diameter was 3.3 cm/m². The average ASI-AAO was 2.7±0.6 cm/m² (Figures 1 and 2). In this group, the aortic root size index was 2.3±0.4 cm/m². Four subjects had echocardiograms performed within 2 months of their dissection (mean=50 days). In those individuals, the mean ASI-AAO was 3.1 cm/m².

In the 2 individuals with spontaneous type B aortic dissections, the ASI-aortic root was 2 and 2.1 cm/m² (cases

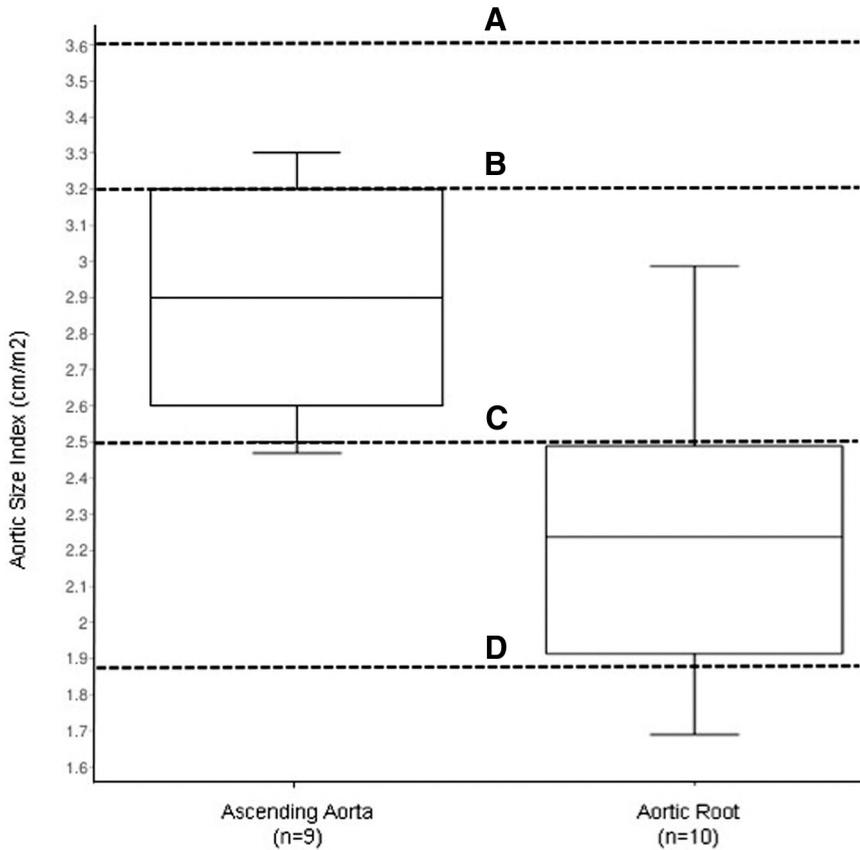


Figure 1. Aortic root and ascending aorta size index in subjects with ascending aorta dissections. Box plot shows median, minimum, maximum, and first and third quartiles. To provide a frame of reference for absolute aortic measurements the ASI-AAO was computed based on the previously reported average BSA of nondissection TS women (1.54 m²).⁸ Dashed line (A) indicates a diameter of 5.5 cm (ASI-AAO=3.6), B indicates a diameter of 5 cm (ASI-AAO=3.2), C indicates a diameter of 3.9 cm (ASI-AAO=2.5), and D indicates a diameter of 2.9 cm (ASI-AAO=1.89), which is the reported value for nondissection TS women.⁹ ASI-AAO indicates aortic size index- ascending aorta; BSA, body surface area.

11 and 20), and, in case 20, the ASI-AAO was 1.9 cm/m² (not available for case 11).

Growth Rate

Figure 2 demonstrates the available echocardiographic measurements of the ASI-AAO among 9 individuals who had a type A dissection ASI growth rates were calculated by using linear mixed-model regression. The mean ASI-AAO growth rate was 0.085 cm/m² per year (95% confidence interval, -0.11 to 0.82). This result suggests that a significant increase in the aortic growth velocity cannot be established in this small group because the 95% confidence interval of the growth rate contains a zero value.

Discussion

The results of this study indicate that individuals with TS and BAV experience aortic dissection at a young age and at considerably smaller aortic diameters than those who develop aortic dissection in the general population. Previous studies have suggested that risk is better predicted by relative aortic size rather than absolute aortic size; therefore, correcting the aortic diameter for the calculated BSA (the ASI) has been proposed.⁴ This correction is critical in the TS population because a hallmark of the syndrome is short stature. In the ITSAD registry, the mean ASI-AAO of subjects with available measurements was 2.7±0.6 cm/m². Matura et al⁸ found

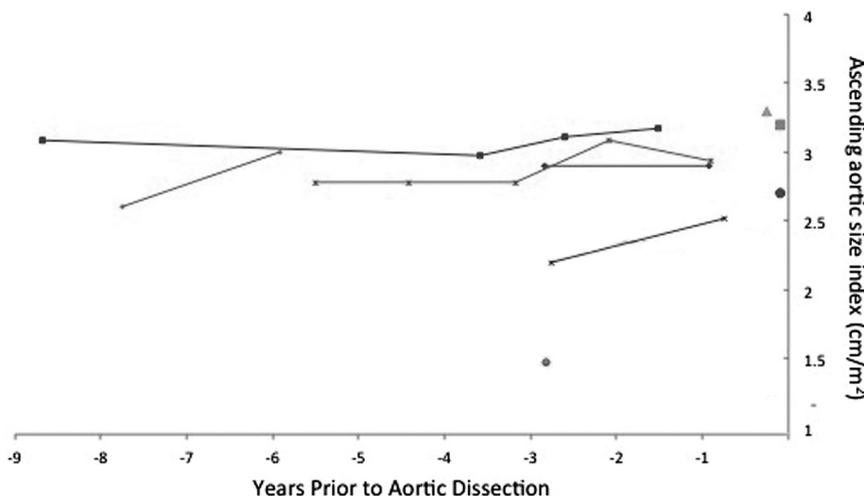


Figure 2. Ascending aorta size index measured by transthoracic echocardiography among 9 individuals before their ascending aortic dissection. Lines are serial measurements in 5 subjects.

that the 95th percentile of the ASI-AAO in 166 TS women without dissection is 1.96 cm/m² (mean, 1.89±0.34 cm/m²). Consistent with our findings, in that study, the ASI-AAO diameters were >2.5 cm/m² in the 3 TS individuals who had dissection. The data from the ITSAD registry support the conclusion of Matura et al⁸ that an ASI of >2.5 cm/m² should prompt clinicians to consider an aortic operation to prevent aortic dissection.

In contrast, Davies et al⁴ stratified risk in 805 non-TS subjects who had either genetically triggered aortopathy or aortopathy syndromes. Davies et al demonstrated that those with an ASI-AAO of ≤2.75 cm/m² had a ≈4%/y dissection risk. In absolute terms, the mean ascending aortic measurement in women with TS who had aortic dissection in the present study was 4.1 cm, which is well below the 5.5-cm threshold proposed to proceed with prophylactic aortic surgery in the general population and significantly lower than the 5.0-cm threshold recommended for those with Marfan syndrome or BAV.⁹

Aortic Growth Rate as a Risk Factor

In patients with connective tissue disorders associated with an increased incidence of aortic dissection such as Marfan or Loeys-Dietz syndrome, the rate of ascending aortic dilatation is predictive of dissection.¹⁰ Based on these findings, patients with Loeys-Dietz and Marfan syndromes who have a diameter of 4.5 to 5 cm at the aortic root or rate of increase >0.5 cm/y are referred for surgical intervention to prevent further progression and dissection.¹¹ Lanzarini et al¹² failed to identify progressive aortic dilation on serial echocardiographic measurements of the aortas of 78 TS patients over a median of 3 years of follow-up. However, that study did not have a dissection cohort for comparison. Among the small group of 5 ITSAD registry subjects with available serial echocardiographic measurements, we could not identify a change in their ascending aorta diameters. Although an increasing growth velocity of the aortic diameter is always concerning, these data suggest that aortic dissection can occur in the setting of normal aortic growth rate.

Other Risk Factors

Patients with TS have an increased prevalence of BAV, hypertension, and aortic coarctation, which are established risk factors for aortic aneurysm and dissection. Indeed, 95% (18/19) of our subjects who experienced spontaneous aortic dissection in the ITSAD registry also had a BAV. BAV is associated with a 9-fold increased risk of aortic dissection in otherwise genetically healthy-appearing individuals.¹³ Although TS alone is an independent risk factor for aortic enlargement, a concomitant BAV has an incremental effect on aortic dimensions at multiple levels and thus probably contributes to the risk for dissection.¹⁴ It is important to recognize, however, that ≈30% of all those with TS have BAV.^{14,15}

The common occurrence of BAV in this group of TS individuals suggests that those without BAV have a markedly reduced risk for dissection. Importantly, 1 subject in our study (1/19, 5%) who experienced aortic dissection had a

completely normal aortic valve, no other structural cardiac disease at autopsy, and no clinical evidence for hypertension. Our previous review of the case literature describing 87 TS individuals with aortic dissection failed to find structural heart disease or hypertension ≈10% of cases.¹ Aortic enlargement and dissection in otherwise completely healthy TS individuals adds further evidence to the theory that there is a fundamental large-vessel arteriopathy associated with the TS phenotype.^{14,16} In this regard, there has been concern that individuals with TS are at greater risk from balloon angioplasty procedures. There was a single case in the ITSAD registry of type B dissection that occurred during placement of a stent for coarctation (case 14). However, a recent review of outcomes in a large multi-institutional study found no deaths among 29 coarctation angioplasty/stenting procedures in TS.¹⁷

One subject in the ITSAD registry experience an aortic dissection during pregnancy and 2 others had pregnancies before dissection. Approximately 0.5% of TS individuals become pregnant spontaneously.¹⁸ In the ITSAD registry, 1 of the 19 cases of the spontaneous aortic dissection (≈5%) occurred during pregnancy. Furthermore, the significance of a remote history of pregnancy is unclear. Two cases of pregnancy-associated aortic dissection were recently reported,¹⁹ and a review of the previous literature review describes 7 additional cases.¹ In those 7 cases, the pregnancies were the result of assisted reproductive therapy. In 6 of the cases, the dissection occurred during pregnancy, and, in 1 case, it occurred 1 year after assisted reproductive therapy. Maternal death occurred in 86% of those who had dissections. The new case described in this study (case 11) brings the total number of reported dissections during assisted TS pregnancies to 10. Assessment of the incremental dissection risk caused by pregnancy is problematic, because the total number of TS pregnancies is not well known. Aortic dissection is estimated to occur in at least 2% of TS pregnancies.^{19,20} Given the vanishingly small risk of aortic dissection in non-TS pregnancy,²¹ the relative risk for dissection for those with TS who become pregnant is considerable. In addition, there is recent evidence that <40% of TS pregnancies are associated with a completely normal fetal-maternal outcome.¹⁹ Therefore, we agree with the recent guideline published by the American Society of Reproductive Medicine that pregnancy is an absolute contraindication for those with TS and a documented cardiac anomaly and that those with no cardiovascular disease are at high risk and require “careful observation and frequent formal monitoring throughout gestation and postpartum.”²²

Strengths and Limitations

This registry represents the largest single group of TS patients who have had a dissection with accurate medical records to confirm the diagnosis and identify the clinical features associated with aortic dissection. Medical records were obtained on all of the subjects in the registry to confirm the presence and type of congenital heart disease, the presence of hypertension, and other important medical history that may be associated with TS and aortic dissection. The study is

limited in its voluntary nature and inherent selection bias. Thus, it is possible that dissections occurring during the study period were missed. Aortic measurements in the dissection population were obtained from echocardiogram reports and were not directly measured by us. Finally, only 4 of the 10 individuals for whom ASI-AAO was known before dissection had echocardiograms within 2 months of the event. We cannot exclude the possibility that progressive aortic enlargement occurred for the other 6 individuals after the most recent echocardiogram. However, this is the first and only study to provide any serial echocardiographic data in TS individuals with aortic dissection. We await the accrual of subjects to the ITSAD registry that may help to validate these preliminary observations.

Conclusion

Aortic dissection is a rare but often catastrophic malady in individuals with TS. It occurs in younger individuals and at significantly smaller aortic diameters than in the general population. The profile of those who have dissections includes an age of >18 years, the presence of BAV, and typical symptoms >24 hours before presentation in >50% of the individuals. The absence of BAV appears to markedly reduce the risk of aortic dissection, but it does not eliminate it. The fact that death occurs in many younger TS women who have symptoms for >24 hours before they seek medical attention emphasizes the need to increase awareness of the critical significance of chest pain in young TS women.

The ideal timing for interventions to protect TS individuals at risk is unknown. In other aortopathy syndromes that are better studied, such as those with Marfan syndrome, surgical intervention is postponed unless a significant change in the aortic growth velocity is documented, or until the absolute aortic diameter is >4.5 cm, a diameter that is larger than most of the patients in the ITSAD registry. Our results suggest that, in TS, a stable growth velocity may not be a reassuring finding. We agree with Matura et al⁸ that, in TS individuals >18 years of age, ASI-AAO >2.5 cm/m² may be an indication for preventive operative intervention.

Acknowledgments

The authors thank Dr Thuan Nguyen for additional biostatistical analysis and her helpful comments and Krista Bever for technical assistance.

Sources of Funding

This study was funded by the Turner Syndrome Society of the United States (TSSUS), Genentech Center for Clinical Research (San Francisco, CA), the Eli Lilly Company (Indianapolis, IN), Oregon Clinical and Translational Research Institute (OCTRI), grant UL1 RR024140 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research (to Drs Airhard and Nguyen).

Disclosures

None.

References

- Carlson M, Silberbach M. Dissection of the aorta in turner syndrome: two cases and review of 85 cases in the literature. *J Med Genet.* 2007;44:745–749.
- Gravholt CH, Landin-Wilhelmsen K, Stochholm K, Hjerrild BE, Ledet T, Djurhuus CB, Sylven L, Baandrup U, Kristensen BO, Christiansen JS. Clinical and epidemiological description of aortic dissection in turner's syndrome. *Cardiol Young.* 2006;16:430–436.
- Nienaber CA, Fattori R, Mehta RH, Richartz BM, Evangelista A, Petzsch M, Cooper JV, Januzzi JL, Ince H, Sechtem U, Bossone E, Fang J, Smith DE, Isselbacher EM, Pape LA, Eagle KA, on Behalf of the International Registry of Acute Aortic D. Gender-related differences in acute aortic dissection. *Circulation.* 2004;109:3014–3021.
- Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B, Coe MP, Kopf GS, Elefteriades JA. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. *Ann Thorac Surg.* 2006;81:169–177.
- Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr.* 1978;93:62–66.
- Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, Lai WW, Geva T. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the pediatric measurements writing group of the American Society of Echocardiography Pediatric and congenital Heart Disease Council. *J Am Soc Echocardiogr.* 2010;23:465–495; quiz 576–467.
- Daily PO, Trueblood HW, Stinson EB, Wuerflein RD, Shumway NE. Management of acute aortic dissections. *Ann Thorac Surg.* 1970;10:237–247.
- Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in turner syndrome. *Circulation.* 2007;116:1663–1670.
- Bonow RO, Carabello BA, Chatterjee K, de Leon JAC, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith JSC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2006;48:e1–e148.
- Legget ME, Unger TA, O'Sullivan CK, Zwink TR, Bennett RL, Byers PH, Otto CM. Aortic root complications in Marfan's syndrome: identification of a lower risk group. *Heart.* 1996;75:389–395.
- Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation.* 2010;121:e266–e369.
- Lanzarini L, Larizza D, Prete G, Calcaterra V, Klersy C. Prospective evaluation of aortic dimensions in turner syndrome: a 2-dimensional echocardiographic study. *J Am Soc Echocardiogr.* 2007;20:307–313.
- Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. 1984;53:849–855.
- Lopez L, Arheart KL, Colan SD, Stein NS, Lopez-Mitnik G, Lin AE, Reller MD, Ventura R, Silberbach M. Turner syndrome is an independent risk factor for aortic dilation in the young. *Pediatrics.* 2008;121:e1622–e1627.
- Sybert VP. Cardiovascular malformations and complications in turner syndrome. *Pediatrics.* 1998;101:e11.
- Ostberg JE, Donald AE, Halcox JP, Storry C, McCarthy C, Conway GS. Vasculopathy in turner syndrome: arterial dilatation and intimal

- thickening without endothelial dysfunction. *J Clin Endocrinol Metab.* 2005;90:5161–5166.
17. Madriago E, Nguyen T, McFerson M, Larson EV, Airhart N, Moller JH, Silberbach M. Frequency and outcomes of cardiac operations and catheter interventions in turner syndrome. *Am J Cardiol.* 2012;110:580–585.
 18. Hovatta O. Pregnancies in women with Turner's syndrome. *Ann Med.* 1999;31:106–110.
 19. Chevalier N, Letur H, Lelannou D, Ohl J, Cornet D, Chalas-Boissonnas C, Frydman R, Catteau-Jonard S, Greck-Chassain T, Papaxanthos-Roche A, Dulucq MC, Couet ML, Cedrin-Dumerin I, Pouly JL, Fenichel P. Materno-fetal cardiovascular complications in turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *J Clin Endocrinol Metab.* 2011;96:E260–E267.
 20. Karnis MF, Zimon AE, Lalwani SI, Timmreck LS, Klipstein S, Reindollar RH. Risk of death in pregnancy achieved through oocyte donation in patients with turner syndrome: a national survey. *Fertil Steril.* 2003;80:498–501.
 21. Oskoui R, Lindsay J Jr. Aortic dissection in women <40 years of age and the unimportance of pregnancy. *Am J Cardiol.* 1994;73:821–823.
 22. Practice Committee of the American Society of Reproductive Medicine. Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. *Fertil Steril.* 2012;97:282–284.

CLINICAL PERSPECTIVE

Aortic dissection and rupture occurs in young women with Turner syndrome. Although this observation is reiterated in case reports, the rarity of its occurrence has limited the availability of information about the natural history and the clinical picture of aortic dissection in Turner syndrome. We estimated that it would require 50 000 patient-years in a prospective longitudinal study to accumulate data similar to the data obtained from the 20 cases we describe from the International Turner Syndrome Aortic Dissection registry. We show that aortic dissection can occur in individuals with Turner syndrome who have no other documented cardiovascular problems. Pregnancy was associated with 1 of 19 subjects in the International Turner Syndrome Aortic Dissection registry, which is 10 times more common than in the general TS population. Bicuspid aortic valve occurred in 95% of the subjects, but it also occurs commonly in those without aortic dissection. We found that aortic dissection in Turner syndrome occurs at a significantly smaller aortic size than in other genetically triggered aortopathies. Data from 5 individuals with serial echocardiographic measurements obtained before their aortic dissection indicates that a stable ascending aortic size over time may not be a reassuring finding. We conclude that an ascending aortic size index $>2.5 \text{ cm/m}^2$ is a significant risk factor for aortic dissection in those with Turner syndrome.