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

Running title: Carlson et al.; Aortic dissection in Turner syndrome

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Abstract:

**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 has received little attention.

**Methods and Results** - We obtained medical records from 20 individuals who voluntarily participated in the International Turner Syndrome Aortic Dissection (ITSAD) Registry. Type-A dissections occurred in 17/20 (85%) and type-B occurred in 3 cases where 1 occurred after coarctation stent placement. Of those with spontaneous aortic dissections, 18/19 (95%) had an associated cardiac malformation that included a bicuspid aortic valve. In one individual, there was no predisposing finding other than having Turner syndrome. Associated pregnancy was documented in 1/19 (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 (ASI-AAO) was 2.7 ± 0.6 cm/m² (n=9).

**Conclusions** - Aortic dissection in TS occurs in young individuals at smaller aortic diameters than 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 TS without cardiac malformations or hypertension. TS individuals > 18 years with an ASI-AAO above 2.5 cm/m² should be considered for an aortic operation to prevent aortic dissection.

**Key words:** aorta; aortic dissection; outcome; sudden death; Turner syndrome
Introduction

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 (FTAAD), 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 six times more common in the TS population compared to the general population.\(^2\) It also occurs at a much younger age in the TS population compared to the general population. The average age at dissection in the TS population is 30.7\(^1\) years compared to 68 years\(^3\) 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.

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.Turner syndrome.org/) and by word of mouth from 2005-2010. Survivors themselves, or individuals aware of a TS dissection were either mailed a questionnaire or completed it directly on the TSSUS website. The questionnaire was used to screen subjects so that all those enrolled in the registry had both Turner syndrome and an aortic dissection. Enrollees were asked...
to sign medical release forms which 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 Turner syndrome. 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.

**Questionnaire**

Each subject with TS or her parent completed a standardized questionnaire regarding karyotype, 45,X or non-45,X (non-45,X incudes a variety of other TS chromosomal arrangements), history of heart disease, prior cardiac surgery, hypertension, growth hormone (GH) 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 in order to compute the aortic size index (ASI). ASI was computed by dividing the size of the aortic root or ascending aorta by the body surface area (BSA). All available echocardiogram reports were reviewed. The data from each report included the date of the echocardiogram, the patient’s height, weight and/or 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 sino-tubular junction and proximal to the innominate as recently described6 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 aortic size index at the level of the ascending aorta.

Results

Aortic dissections occurred in 20 individuals between 1988 and 2010 with the median year of 2004 (Table 1). Seventeen of the 20 registry subjects had a Stanford type-A aortic dissection7 and three patients developed a type-B dissection (cases 11, 14, 20). In one subject (case #14) a type-B dissection occurred in the cardiac catheterization laboratory during stent placement for coarctation of the aorta. Her datum was not included in further comparisons. Thus among the entire cohort of those with spontaneous aortic dissections only 2/19 (11%) had type-B aortic dissection.

The average age at the time of dissection was 31.5 years ± 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 (CHD) found during autopsy. All of the 18 subjects with CHD had a
Symptoms and survival in patients with spontaneous dissection (Table 1)

All but one subject, (1/19, 5%) had symptoms prior to death or operation. One subject (1/19, 5%) died 1 hour after the onset of chest pain. Five additional subjects (5/19, 26%) reported symptoms between 1-24 hours prior to presentation, but 13 subjects (13/19, 68%) had symptoms for >24 hours prior to presentation. The most common symptoms were chest pain as reported by 16/19 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 likelihood of survival (30% > 24 hours versus 50% < 24 hours, Fisher’s 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 symptoms. 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 prior to presentation and 7 died (78%).
Pregnancy

Three registry subjects had a history of pregnancy prior to their aortic dissection (case # 6, 11, 20). In one instance (case #19) a successful pregnancy and delivery occurred 2 years after the aortic dissection. Of the 3 who were pregnant prior to dissection, one underwent assisted reproductive therapy (case #11) in the others (case # 6 and 20) the pregnancies occurred spontaneously in individuals with mosaic karyotypes. Two of these subjects had spontaneous type-B dissections (case #11 & 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 had a type-A dissection. Her ascending aorta was found to be 3.3 cm/m2 that was the largest echo diameter of the ascending aorta reported in this study. The echo study was performed 90 days prior to 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 CT and echocardiography 8 years prior to the pregnancy. She underwent assisted reproductive therapy (ART) with implantation of two embryos. Symptoms occurred at 36 weeks gestation and maternal death followed an emergent cesarean section in which 2 healthy infants were delivered. Post-mortem 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 prior to the event. A CT 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 to 5; mean total follow-up time 733 days). 2 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 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 # 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 using linear mixed model regression. The mean ASI-AAO growth rate was 0.085 cm/m2/year (95%CI -0.11 to 0.82). This result suggests that a significant increase in the aortic growth velocity cannot be established in this small group since the 95% CI of the growth rate contains a zero value.

**Discussion**

The results of this study indicate that individuals with Turner syndrome 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 risk is better predicted by relative aortic size rather than absolute aortic size, therefore, correcting the aortic
diameter for the calculated BSA (the aortic size index, ASI) has been proposed.\textsuperscript{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/m\textsuperscript{2}. Matura et al\textsuperscript{8} found the 95th percentile of the ASI-AAO in 166 TS women without dissection to be 1.96 cm/m\textsuperscript{2} (mean 1.89 ± 0.34 cm/m\textsuperscript{2}). Consistent with our findings, in that study the ASI-AAO diameters were greater than 2.5 cm/m\textsuperscript{2} in the 3 TS individuals who had dissection. The data from the ITSAD registry supports the conclusion of Matura et al that an aortic size index of > 2.5 cm/m\textsuperscript{2} should prompt clinicians to consider an aortic operation to prevent aortic dissection.

In contrast, Davies et al\textsuperscript{4} stratified risk in 805 non-Turner syndrome subjects who had either genetically triggered aortopathy or aortopathy syndromes. Davies et al demonstrated that those with an ASI-AAO of 2.75 cm/m\textsuperscript{2} or less had a ~ 4%/year 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.\textsuperscript{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.\textsuperscript{10} Based on these findings, patients with Loeys-Dietz and Marfan syndromes who have a diameter of 4.5-5 cm at the aortic root or rate of increase greater than 0.5 cm/yr are referred for surgical intervention to prevent further progression and dissection.\textsuperscript{11} Lanzarini et al.\textsuperscript{12} failed to identify progressive aortic dilation on serial echocardiographic
measurements of the aortas of 78 Turner 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 five ITSAD registry subjects with available serial echocardiographic measurements we could not identify a change in there ascending aorta diameters. While 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 that 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 normal-appearing individuals.13 While 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 approximately 30% of all those with TS have BAV.15 14

The common occurrence of BAV in this group of TS individuals suggests that those without BAV have a markedly reduced risk for dissection. Importantly, one subject in our study (1/19, 5%) who suffered 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 Turner individuals with aortic dissection failed to find structural heart disease or hypertension in approximately 10% of cases.16 Aortic enlargement and dissection in otherwise completely healthy Turner individuals adds further evidence to the theory that there is a fundamental large-vessel arteriopathy associated with the Turner
phenotype. In this regard, there has been concern that individuals with Turner syndrome 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 Turner syndrome.

One subject in the ITSAD registry suffered from an aortic dissection during pregnancy and 2 others had pregnancies prior to dissection. Approximately 0.5% of TS individuals become pregnant spontaneously. 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 and a review of the previous literature review describes 7 additional cases. In those 7 cases, the pregnancies were the result of assisted reproductive therapy (ART). In six of the cases the dissection occurred during pregnancy, and in one case it occurred 1 year after ART. Maternal death occurred in 86% of those who dissected. The new case described in this study (#11) brings the total number of reported dissections during assisted Turner pregnancies to 10. Assessment of the incremental dissection risk caused by pregnancy is problematic since the total number of Turner pregnancies is not well known. Aortic dissection is estimated to occur in at least 2% of Turner pregnancies. Given the vanishingly small risk of aortic dissection in non-Turner pregnancy the relative risk for dissection for those with Turner syndrome who become pregnant is considerable. In addition, there is recent evidence that fewer than 40% of Turner pregnancies are associated with a completely normal fetal-maternal outcome. 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.”

Strengths/Limitations

This registry represents the largest single group of TS patients that 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 prior to 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 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 the general population. The profile of those who dissect include age > 18 years, presence of BAV, and typical symptoms > 24 hours prior to presentation in more than half of the individuals. The absence of BAV
appears to markedly reduce the risk of aortic dissection but does not eliminate it. The fact that death occurs in many younger TS women who have symptoms for more than 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 Turner 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 greater than 4.5 cm, a diameter that is larger than most of the patients in the ITSAD registry. Our results suggest that in Turner syndrome a stable growth velocity may not be a reassuring finding. We agree with Matura et al.\textsuperscript{8} that in Turner individuals \textgreater\ 18 years of age ASI-AAO \textgreater\ 2.5 cm/m2 may be an indication for preventive operative intervention.

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Conflict of Interest Disclosures: None.

References:


Table 1. Dissection registry subjects

<table>
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<th>Patient #</th>
<th>Age at dissection, y</th>
<th>Cardiac diagnosis (comment)</th>
<th>Hypertension (Y/N)</th>
<th>Most recent Ao measurement (cm)</th>
<th>ASI</th>
<th>Location of dissection</th>
<th>Symptom duration</th>
<th>Outcome</th>
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<td>1</td>
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<td>N</td>
<td>Aortic Root: 2.6</td>
<td>2</td>
<td>Type A</td>
<td>&gt; 24 hr</td>
<td>Death</td>
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<tr>
<td>2</td>
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<td>Y</td>
<td>Asc Ao: 3.2*</td>
<td>2.5*</td>
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<td>&gt; 24 hr</td>
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<td>3</td>
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<td>3*</td>
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<td>&gt; 24 hr</td>
<td>Death</td>
</tr>
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<td>&gt; 24 hr</td>
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<td>&gt; 24 hr</td>
<td>Death</td>
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<td>40</td>
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<td>&gt; 24 hr</td>
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**Not previously reported, reference is given for known prior reports others may or may not have been reported
AS=aortic stenosis, BAV = bicuspid aortic valve, IAA=interrupted aortic arch, VSD=ventricular septal defect, RSA=right subclavian artery
Figure Legends:

Figure 1. Aortic root and ascending aorta size index in subjects with ascending aorta dissections. Box plot shows median, minimum, maximum, first and third quartile. To provide a frame of reference for absolute aortic measurements the ASI-AAO was computed based on the previously reported average BSA of non-dissection TS women (1.54 m2). 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 non-dissection TS women.

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