

Spectrum of cardiovascular abnormalities in Turner syndrome

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Abstract. Haploinsufficiency for the X-chromosome in females has important and multifaceted effects upon the cardiovascular system. Girls with Turner syndrome (TS) may demonstrate anatomic malformations affecting the heart, aorta and other major vessels, hypertension and abnormalities of heart rate, cardiac conduction and repolarization. The aorta is dilated in almost 50% of patients and aortic deterioration with aneurysm, dissection and rupture occurs with increased frequency in young and middle-aged patients. Finally many women with TS experience premature onset of coronary artery disease. This chapter reviews the more recent scientific literature regarding these abnormalities. Published by Elsevier B.V.

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1. Congenital cardiovascular malformations

Cardiovascular malformations including left heart and aortic hypoplasia and aortic coarctation are common and result in a very high mortality rate for 45,X fetuses [1–3]. Cardiovascular failure and hydrops are usually associated with obstructed jugular lymphatics with large nuchal cystic hygromata [1,4]. These hygromata resolve as the lymphatics open later in gestation, but residual postnatal webbing of the neck predicts defects such as bicuspid aortic valve (BAV) and aortic coarctation in surviving

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individuals with TS [5–7]. The statistical association between nuchal hygromata and coarctation and BAV in TS led to the hypothesis that dilated lymphatics cause the cardiovascular defects by compressing outflow tracts [5]. This theory does not account for the presence of aortic coarctation and BAV in TS patients without evidence of fetal lymphedema [6], and the association is not found in other disorders characterized by fetal cystic hygromata and congenital heart disease, e.g., Noonan syndrome [8]. A different theory was suggested by Miyabara et al. emphasizing the involvement of the specific portion of the aorta that is derived from the 4th branchial arch, and also the reduction in thymic size noted in many fetuses with TS [3,4], thus implicating a neural crest defect in the cardiovascular malformations in TS, similar to the DiGeorge syndrome. However, typical heart defects in that syndrome are tetralogy of Fallot and truncus arteriosus, which are not seen in TS, and patients with DiGeorge syndrome have clinically significant immunodeficiency, also not found in TS. In contrast, Barr et al. noted a uniform reduction in cardiac size in TS fetuses, independent of specific malformations, and suggested that impaired myocardial growth is a primary feature of TS cardiovascular deficiencies [4]. This does not account for the various anatomical anomalies and cardiac size does not generally appear reduced in liveborn individuals with TS.

1.1. Aortic coarctation and bicuspid aortic valve (BAV)

Aortic coarctation and BAV seem to be the most common, clinically significant anatomic defects in live born individuals with TS. Several large imaging studies of unselected TS populations have been reported in the past few years. Averaging results from these studies estimates ~11% with aortic coarctation and ~16% with BAV [6,9–12]. Coarctation may be diagnosed in older children and adults as well as infants with TS, and magnetic resonance imaging may identify cases missed by echocardiography [11,13–16]. MR imaging also detects an elongation of the aortic arch with prominent kinking past the site of the ductus insertion, termed elongated transverse arch (ETA) [17] in almost 50% of patients with TS. This distinctive anatomy is embryologically similar to coarctation, was termed pseudocoarctation in the past, and has been associated with dissection [18]. Thus, a range of aortic stricture is found in TS, with variable hemodynamic effects, but with potential relation to aortic deterioration.

The abnormal aortic valve in TS is often clinically silent and detected only during screening [19]. The range of aortic valve pathology found in TS is similar to that in isolated congenital BAV, with complete or partial fusion of right- and left-coronary leaflets the most common variant. The risks associated with BAV in TS are thought to be similar to those for non-syndromic cases. The abnormal valve is prone to infective endocarditis, and may deteriorate over time, leading to aortic stenosis or regurgitation. The BAV is associated with aortic wall abnormalities, including ascending aortic dilation, aneurysm formation and aortic dissection [20,21]. It is interesting to note that BAV is found in ~1–2% of the general population, with a 3:1 male/female ratio, suggesting that monosomy for the X-chromosome is a predisposing factor. An increase in the prevalence of ASD and VSD has only been reported in Italy [22].

1.2. Venous abnormalities

After ETA, aortic coarctation and BAV, the next most common cardiovascular anomalies in TS are partial anomalous pulmonary venous connection (PAPVC) and persistent left superior vena cava, each found in 13% of adults by MR angiography [17] and anatomic study of fetal cases [3]. BAV and PAPVC have the highest relative risk (RR) (3603- and 1293-fold, respectively) compared to the general population [12]. PAPVC appears to be clinically significant in about 50% of TS cases, and may not become symptomatic until adulthood [23–25].

2. Aortic disease

A potentially fatal consequence of X-chromosome deletion is the risk for aortic aneurysm, dissection or rupture. At issue is whether, apart from specific congenital defects such as BAV and coarctation, or systemic hypertension, there is an intrinsic weakness of the vascular wall along the lines of Marfan syndrome that would constitute additional risk for aortic dilation and dissection.

2.1. Aortic dissection

To date there have been 73 reported cases of aortic dissection or rupture in individuals with TS ages 4–64 years [19,26–31]. The best epidemiological information is from a very recent Danish Registry study [30] that reports an overall incidence of 36 cases/100,000 patient-years for TS vs. 6/100,000 general population, and for the 30–40 years age group the rate is 78 cases/100,000 patient-years for TS vs. <1 for all others. The average age at dissection was 35, with a range of 18–61 years. Of the entire group of TS women with dissection in the Danish study, 25%, were normotensive without BAV or coarctation and thus apparently had zero risk factors for aortic dissection apart from the diagnosis of TS. Sybert reviewed 45 TS cases of aortic dissection published through 1997 [19]. Ages ranged from 4 to 64 years, with an average of 28 years and ~10% had neither BAV nor coarctation nor hypertension. Thus it seems that 10–25% of girls and women with aortic dissection have no apparent risk factor for aortic dilation or dissection other than TS. Moreover, while BAV and hypertension are major risk factors for aortopathy in the general population, dissection related to these pathologies occurs much later in life, typically in the seventies in women, while the average age of dissection in TS females with BAV or hypertension is between the ages of 25 and 35.

2.2. Vasculopathy

Dilation of the ascending aorta is found in 40–50% of girls and women with TS [11,13,21,32,33]. Because of their small size, aortic diameters that are considered normal in normal height, age-matched females may actually be enlarged in individuals with TS making aortic measurements in individuals with TS difficult to interpret. These diameters should be indexed for body surface area [11,34]. The aortic profile in individuals with TS is similar to individuals with isolated congenital BAV with the area of greatest dilatation often

occurring in the ascending aorta above the sinotubular junction. MR imaging can be a useful adjunct to echocardiography for determining aortic dimensions in individuals with TS. Aortic dilation is associated with the presence of a BAV, aortic coarctation and hypertension, but is often found in individuals with none of these factors. In addition, there is an altered distensibility of the aorta in TS [32,33] and enlargement of other large vessels including brachial and carotid arteries [33,35], suggesting a general vasculopathy perhaps related to some connective tissue defect in the syndrome. In many cases where pathology is available, cystic medial necrosis and tissue friability have been reported [19,31,28] similar to that found in Marfan syndrome and the altered compliance of the arterial wall has also been likened to findings in Marfan syndrome [32]. Other signs of connective tissue disorder, such as joint laxity, have not been found in TS.

3. Abnormalities of cardiac rate, conduction and repolarization

Resting tachycardia is noted in many girls and women with TS, even beginning in utero [36]. This observation, together with the frequent elevations in systemic BP has led to the hypothesis of altered autonomic nervous system (ANS) activity in this disorder. One study documented a relatively higher heart rate and systolic BP in young women with TS compared to age-matched controls, and a higher level of resting norepinephrine in TS [37]. This study also found a compromised response to sympathetic stimulation in the TS group, and concluded that there is a deregulation of the sympathetic nervous system in TS [37]. Another small study investigated heart rate variability in young adults with TS and reported relatively diminished low frequency power and concluded that there is decreased sympathovagal balance in TS [38].

Girls and women with TS have a high prevalence of electrocardiographic conduction and repolarization abnormalities. Right axis deviation, T wave abnormalities, accelerated AV conduction and QTc prolongation are significantly more common in women with TS than normal, age-matched controls [39]. The right axis deviation may be associated with underlying PAPVC or related defects affecting the right heart, but the other findings appear independent from anatomic defects [39]. It is interesting that despite the often cited preponderance of left-sided, obstructive defects in TS, left ventricular hypertrophy or other left-sided abnormalities are not particularly frequent in TS ECGs. Taken together with a resting tachycardia, elevated BP and impaired sympathovagal tone [37,38], it seems that there may be an intrinsic defect in autonomic regulation of the cardiovascular system in TS. The clinical significance of these recent observations remains to be determined, but more vigilant monitoring of ECGs in TS seems warranted. Patients with Marfan syndrome are also noted to have abnormal ECG with prolonged QT and possibly increased risk for arrhythmic sudden death [40,41].

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