Imaging of cardiovascular risk in patients with Turner's syndrome

Citation for published version:
Marin, A, Weir-McCall, JR, Webb, DJ, van Beek, EJR & Mirsadraee, S 2015, 'Imaging of cardiovascular risk in patients with Turner's syndrome' Clinical Radiology. DOI: 10.1016/j.crad.2015.03.009

Digital Object Identifier (DOI):
10.1016/j.crad.2015.03.009

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published in:
Clinical Radiology

Publisher Rights Statement:
This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Imaging of cardiovascular risk in patients with Turner’s syndrome

A. Marin a, J.R. Weir-McCall b, D.J. Webb c, E.J.R. van Beek a, S. Mirsadraee a, *,

a Clinical Research Imaging Centre, Queen’s Medical Research Institute, University of Edinburgh, Edinburgh EH16 4TJ, UK
b Division of Cardiovascular and Diabetes Medicine, Ninewells Hospital & Medical School, Dundee DD1 9SY, UK
c Queen’s Medical Research Institute, University of Edinburgh/BHF Centre for Cardiovascular Science, Edinburgh EH16 4TJ, UK

Article history:
Received 17 December 2014
Received in revised form
17 February 2015
Accepted 19 March 2015

Turner’s syndrome is a disorder defined by an absent or structurally abnormal second X chromosome and affects around 1 in 2000 newborn females. The standardised mortality ratio in Turner’s syndrome is around three-times higher than in the general female population, mainly as a result of cardiovascular disorders. Most striking is the early age at which Turner’s syndrome patients develop the life-threatening complications of cardiovascular disorders compared to the general population. The cardiovascular risk stratification in Turner’s syndrome is challenging and imaging is not systematically used. The aim of this article is to review cardiovascular risks in this group of patients and discuss a systematic imaging approach for early identification of cardiovascular disorders in these patients.

© 2015 The Authors. Published by Elsevier Ltd on behalf of The Royal College of Radiologists. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Turner’s syndrome (TS) or Ullrich–Turner’s syndrome is a disorder defined by an absent or structurally abnormal second X chromosome and affects around 1 in 2000 newborn females. The variable phenotypes can be split into three main categories: monosomy X karyotype (45,X) (in 36–45%); mosaic karyotype (44–54%); and an isochromosome Xq. (5–11%). Short stature, gonadal dysgenesis, and congenital cardiovascular defects are common features of TS. Congenital heart defects, such as hypoplastic left heart syndrome and/or hypoplastic aortas, are the major causes of prenatal mortality. The foetuses with less severe cardiovascular defects survive the first trimester and can be recognised by in-utero ultrasound by hydrops of the trunk and limbs, large and loculated cystic hygromas of the posterolateral neck, pleural effusions, and ascites. When these resolve they leave the postnatal webbing of the neck (pterygium colli), puffy hands and feet, or redundant nuchal skin, making the diagnosis possible in 20–30% of newborn girls with TS. Around one-third are diagnosed in mid-childhood on the investigation of short stature and broad chest. In most other patients, who have milder signs and symptoms of TS, the condition is diagnosed due to delayed or absent pubertal development secondary to gonadal dysgenesis either in adolescence or in adulthood. The most common cardiovascular defects in surviving TS patients are bicuspid aortic valve (BAV) and aortic coarctation. These
patients are also at increased risk for hyperlipidaemia, hypertension, and atherosclerosis.\(^8\)

The age-specific death rate in TS is around three-times higher than in the general female population with Fig 1 tabulating the relative standardised mortality ratios (SMRs).\(^2,3\) Cardiovascular disease accounts for 41% of excess deaths and the relative risk is most markedly elevated with cardiovascular congenital anomalies; in particular BAV and aortic aneurysm.\(^2\) The risk of acquired aortic dissection is increased by up to 100-fold and can occur in TS patients as young as 16–18 years.\(^9,10\)

The above highlights the need for appropriate cardiovascular risk stratification in TS patients. In the UK and some other countries, dedicated TS clinics have been established where teams of paediatric endocrinologists, gynaecologists, cardiologists, radiologists, and hypertension specialists are implementing appropriate screening and management strategies.\(^8,11\) The aim of this paper is to review the role of clinical imaging in TS cardiovascular risk stratification.

Methodology

Literature search

Publications were identified by a systematic literature search using PubMed to identify studies evaluating medical issues in TS published between January 1990 and August 2014. The search terms used in the Medical Subject Headings (MeSH) Database were "Turner Syndrome/complications"[Mesh] OR "Turner Syndrome/etiology"[-Mesh] OR "Turner Syndrome/mortality"[Mesh] OR "Turner Syndrome/radiography"[Mesh] OR "Turner Syndrome/ultrasonography"[Mesh] OR "Turner Syndrome/imaging"[Mesh] OR "Turner Syndrome/cardiovascular"[Mesh] OR "Turner Syndrome/congenital"[Mesh]. Out of the 1242 papers found, 82 met the selection criteria. Only full-length original articles were included. Non-English texts, experimental studies, and case series with fewer than five patients were excluded. In addition, the references were revised and eligible articles that were not captured by the search strategy were identified.

Congenital cardiovascular disorders and complications

Cardiovascular anomalies (Table 1) are present in up to 50% of the TS population and are the major cause of premature mortality.\(^3,5,8,10,12–15\) The most commonly occurring cardiovascular anomalies are a BAV, aortic dilatation, elongation of the thoracic arch, aortic coarctation, and partial anomalous pulmonary venous return.

Pathogenesis

The pathogenesis of these cardiovascular defects is still unclear. Previously, it was thought that the left heart outflow tract defects were caused by increased fetal lymphatic pressure and jugular lymphatic sac obstruction leading to obstruction to or reduction of the blood flow.
within the developing heart, resulting in the observed left heart defects. This hypothesis also encompassed the development of anomalous pulmonary venous drainage due to the hold-up of blood flow within the pulmonary bed secondary to the left heart defects.\textsuperscript{16} However, more recently published papers have demonstrated the presence of aortic coarctation and BAVs in TS without evidence of fetal lymphoedema, and that the presence of partial anomalous pulmonary venous return is not associated with fetal lymphoedema, and that the presence of partial anomalous pulmonary venous return is not associated with either aortic coarctation or BAV, both observations in contradiction to the original hypothesis.\textsuperscript{17,18} Miyabara\textsuperscript{19} and colleagues suggest an alternative idea, that a primary neural crest defect in the region responsible for the formation of the 4\textsuperscript{th} pharyngeal pouch and 4\textsuperscript{th} branchial branch was responsible for both the congenital heart and lymphatic anomalies. Regardless of the exact embryological trigger for the developmental anomalies in TS, presuming a single trigger can account for all of the anomalies, great leaps have been made in the understanding of the genetic determinants of congenital heart defects. Cardiovascular defects, aortic aneurysm, and dissection are most frequently observed among TS patients with 45, X karyotype, with a high prevalence of congenital heart defects also present in TS females missing only the X chromosome short arm, meaning that haplo-insufficiency for Xp genes contributes to the abnormal aortic valve and aortic arch development in TS.\textsuperscript{3,18,20} In the future, this knowledge may allow a more targeted identification of those most likely to benefit from a more detailed or intensive investigation programme.

**Clinical presentations**

BAV is the most common congenital cardiovascular malformation occurring in up to 30\% of TS patients compared with just 1–2\% in the general population (Fig. 2).\textsuperscript{21,22} Individuals with BAV are at increased risk of aortic coarctation and/or aortic dilatation.\textsuperscript{22} BAV at a young age is usually clinically silent, but with age BAV tends to more rapidly degenerate and calcify, resulting in progressive stenosis and/or regurgitation (Fig. 3).\textsuperscript{23,24} In 95\% of adult TS females, BAV is a consequence of fusion of the right and left coronary leaflets (R-L BAV), while the fused right coronary and non-coronary leaflets (R–NC BAV) variant is much less common.\textsuperscript{25} However, a single study of post-mortem heart specimens from 36 TS fetuses and one TS newborn reported a larger proportion of R-NC BAV type (31\%).\textsuperscript{25} The pattern of aortic valve leaflet fusion in patients with BAV may be important, because general population studies have demonstrated that the R-NC BAV is associated with a higher prevalence of significant aortic valve stenosis and regurgitation, whereas the R-L BAV is associated with aortic coarctation, dilatation, and less frequently with aortic valve pathology.\textsuperscript{26,27} Both a genetic and flow-mediated hypothesis have been proposed for the association between BAV and aortopathy.\textsuperscript{28} The genetic model proposes that a disorder in one of the genes responsible for vascular connective tissue development is responsible for both BAV formation and the subsequent propensity for aortic dilatation. However, a growing body of evidence demonstrates an abnormal eccentric flow pattern, which is directed at the lateral ascending aortic wall in those with R-L fusion, resulting in wall remodelling secondary to elevated regional wall shear stress even where there is no significant transvalvular gradient or regurgitation.\textsuperscript{29–31} The role of imaging in BAV is for the detection of fused leaflets, the characterisation of the location of the fusion and the quantification of valvular function. Transthoracic two-dimensional and colour Doppler echocardiography enables a reliable non-irradiating assessment of the

---

**Table 1**

| System     | Congenital anomaly or acquired disease | Frequency/risk | Occurs in combination with |
|------------|---------------------------------------|----------------|----------------------------|
| Cardiovascular | Bicuspid aortic valve | 30\% (versus 1–2\% in general population)\textsuperscript{3,12} | Aortic coarctation, neck webbing\textsuperscript{17} |
|            | Aortic dilatation                      | 32–42\%\textsuperscript{15,39,40} | BAV, aortic coarctation, hypertension or independently |
|            | Aortic dissection                     | 100-fold increased risk, 36 cases/100,000 patient years (versus 6/100,000 in general population)\textsuperscript{9} | BAV, aortic coarctation, hypertension |
|            | Aortic coarctation                    | 10–12\%\textsuperscript{12,69} | BAV, neck webbing\textsuperscript{17} |
|            | Elongated transverse arch             | 49%\textsuperscript{17} | Arterial hypertension, hyperlipidaemia |
|            | Partial anomalous pulmonary venous return | 13%\textsuperscript{17} | |
|            | Ischaemic heart disease               | 50%, appearing 6–13 years earlier than expected\textsuperscript{20} | |
| Skeletal   | Osteoporosis                          | 10–50\%\textsuperscript{70,72} | Prolonged hypogonadism |
|            | Bone fractures                        | 5–45\%\textsuperscript{70,72} | Osteoporosis |
|            | Cervical vertebral hypoplasia         |                      | Growth hormone therapy |
| Renal      | Scoliosis                             | 5–10\%\textsuperscript{27} | |
|            | Cubitus valgus                        | Up to 50\%           | |
|            | Genu valgum                          | 60%\textsuperscript{14} | |
|            | Short metacarpals and metatarsals     |                      | |
|            | “Bayonet deformity” or Madelung’s deformity | 33–38\%\textsuperscript{75,76} | |
| Reproductive | Gonadal dysgenesis                    | 90% require hormone-replacement therapy\textsuperscript{6} | |
cardiovascular anatomy including the aortic valve and root and the ascending part of the thoracic aorta, as well as providing accurate assessment of valvular function. \textsuperscript{32} However, transthoracic echocardiography can be inadequate in visualising the aortic valve in TS in around 6\%, with BAV itself as a risk factor for non-visualisation of the aortic valve. \textsuperscript{33} Other factors for suboptimal visualisation of the aortic valve with transthoracic echocardiography are calcification of the valve and a poor acoustic window (associated with obesity and short stature, both common occurrences in women with TS). \textsuperscript{34,35} In these instances, cardiac MRI is useful for further evaluation of the anatomy of the valve using balanced steady-state free precession (bSSFP) cine sequence to visualise the valve, with phase-contrast MRI for functional assessment. MRI typically underestimates the severity of aortic stenosis compared with echocardiography due to flow vorticity causing signal loss. However, MRI is associated with less inter-scan and interobserver variability. \textsuperscript{36–38}

Aortic dilatation is reported in 32\%–42\% of women with TS. \textsuperscript{15,39,40} Table 2 summarises the studies on aortic dilatation in Turner’s syndrome. Aortic dilatation may occur in isolation. However, it is most commonly found in association with BAV and/or aortic coarctation, with one study showing BAV to be present in 85\% of those with aortic dilatation. \textsuperscript{13,41} Given that age and body size are strongly predictive of aortic diameter, use of standard absolute values for the evaluation and diagnosis of aortic dilatation in TS, with its abnormal body posture, is grossly inaccurate. \textsuperscript{42} Comparison with normograms derived from age-matched women is also flawed for the same reason. \textsuperscript{43} The use of an ascending/descending aortic diameter (AD/DD) ratio circumvents some of these issues as it provides an individualised normative value against which to compare with previous data.

**Figure 2** Systolic cine MRI of the BAV in two patients with TS. (a) Demonstrates a R-L BAV (arrow) and (b) demonstrates a R-L BAV (arrow) with raphe (arrowhead).

**Figure 3** Systolic bSSFP cine MRI of the aortic valve (a), the aortic root (b) and ascending aorta (c,d) in a 45-year-old TS patient with mild aortic stenosis and aortic regurgitation on transthoracic echocardiography, which was unable to assess the aortic dimensions. (a) Atrioventricular view demonstrates a L-R BAV (arrow), and (b) the three-chamber view shows an asymmetric jet flow through the BAV (arrow). (c) Shows the aortic root and ascending aorta in sagittal oblique (diameter measurements white lines) and left bottom figure (white frame) in axial views at the level of the main pulmonary artery.
Table 2
Summary of studies looking at MRI assessment of aortic dilatation and dissection in Turner’s syndrome.

| Study                  | No  | Sequence                  | Measurements                                                                 | Findings                                                                                           |
|------------------------|-----|---------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Dawson-Falk 1992       | 40  | ECG-gated T1W “black blood” TSE sequence | Axial stack through aorta with diameter measured on slice with most dilated aorta | Aortic dilatation in 12.5% (indexed diameter >95th CI based on CT values). 80% of these were only seen on MRI |
| Castro 2002            | 77  | Axial stack through aorta with diameter measured on slice with most dilated aorta | Ascending aortic dilation in 40% (indexed diameter >95th CI based on CT values); 26.7% had AD:DD >1.5 | Ascending aortic dilation in 40% (indexed diameter >95th CI based on CT values); 26.7% had AD:DD >1.5 |
| Ostberg 2004           | 15  | Ascending and descending aorta at level of right pulmonary artery | Ascending aortic dilation in 33% using MRI criteria (AD:DD >1.5), but only 7% met both MRI and echocardiography criteria for dilatation. Dilated root associated with age and BAV 19% (n = 5) had ascending aortic dilation (not defined) |
| Chalard 2005           | 21  | Two axial slices producing four measurements | Article focused on seven case series. n = 1 with aortic dilatation, which developed and progressed during imaging follow-up | Growth hormone has no effect on indexed aortic size |
| Ilyas 2006             | 17  | Transverse plane (no further information provided) | 32% have ASI >2. 9.5% have AD diameter >mean +2 SD of control population, 32% have ASI >2, 45% have AD:DD >1.5 | Good correlation between echo and CMR in ascending aorta, however poorer correlation in rest of aorta. |
| Bondy 2006             | 101 | Ascending and descending aorta at level of RPA | Aortic root dilated (indexed diameter >mean -2 SD) in 25% of patients with BAV compared with 5% of TAV | Aortic root dilated (indexed diameter >mean -2 SD) in 25% of patients with BAV compared with 5% of TAV |
| Matura 2007            | 166 | Five levels within the thoracic aorta and one in the proximal abdominal aorta | No dilatation in mean aortic diameter, however aortic dilatation (indexed diameter >mean +2 SD of control group) was present in n = 5 in at least one of the nine measured locations. Using AD:DD, dilatation was present in 28% of TS and 32% of controls. | No dilatation in mean aortic diameter, however aortic dilatation (indexed diameter >mean +2 SD of control group) was present in n = 5 in at least one of the nine measured locations. Using AD:DD, dilatation was present in 28% of TS and 32% of controls. |
| Lanzarini 2007         | 59  | Four locations in ascending aorta (annulus, sinus, STJ, ascending aorta) | Good correlation between echo and CMR in ascending aorta, however poorer correlation in rest of aorta. | Good correlation between echo and CMR in ascending aorta, however poorer correlation in rest of aorta. |
| Sachdev 2008           | 15  | Four locations in ascending aorta | Aortic root dilated (indexed diameter >mean -2 SD) in 25% of patients with BAV compared with 5% of TAV | Aortic root dilated (indexed diameter >mean -2 SD) in 25% of patients with BAV compared with 5% of TAV |
| Cleeman 2010           | 41  | Nine locations in thoracic aorta | No dilatation in mean aortic diameter, however aortic dilatation (indexed diameter >mean +2 SD of control group) was present in n = 5 in at least one of the nine measured locations. Using AD:DD, dilatation was present in 28% of TS and 32% of controls. | No dilatation in mean aortic diameter, however aortic dilatation (indexed diameter >mean +2 SD of control group) was present in n = 5 in at least one of the nine measured locations. Using AD:DD, dilatation was present in 28% of TS and 32% of controls. |
| Hjerrild 2010          | 102 | Eight locations in thoracic aorta | 23% had aortic dilation (indexed diameter >mean +2 SD) in at least one location, with dilatation in ≥2 locations in 14%. In the latter group, 85% had BAV. Aortic diameter correlated with age, sex, BP, and presence of CoA and BAV. | 23% had aortic dilation (indexed diameter >mean +2 SD) in at least one location, with dilatation in ≥2 locations in 14%. In the latter group, 85% had BAV. Aortic diameter correlated with age, sex, BP, and presence of CoA and BAV. |
| Mortensen 2010         | 99  | Eight locations in thoracic aorta | TS have 6.7X RR of ascending aortic dilatation compared to the general population. Ascending aorta dilatation associated with BAV and aortic coarctation and 45X monosomy. | TS have 6.7X RR of ascending aortic dilatation compared to the general population. Ascending aorta dilatation associated with BAV and aortic coarctation and 45X monosomy. |
| Kim 2011               | 51  | Nine locations in thoracic aorta | Ascending aorta dilatation was common, with 30% with dilated aortic sinus (indexed diameter >mean +2 SD). 40.8% had AD:DD >1.5. | Ascending aorta dilatation was common, with 30% with dilated aortic sinus (indexed diameter >mean +2 SD). 40.8% had AD:DD >1.5. |
| Mortensen 2011         | 80  | Nine locations in thoracic aorta at baseline and 2 yrs follow-up | At a mean follow-up of 2.4 ± 0.4 yrs, increased dilatation was seen in the aortic sinus, sinotubular junction and mid-ascending aorta. Mean growth rate 0.1—0.4 mm/yr. BAV associated with more rapid growth rate than TAV (0.44 ± 0.57 versus 0.18 ± 0.61 mm/yr/m²) | At a mean follow-up of 2.4 ± 0.4 yrs, increased dilatation was seen in the aortic sinus, sinotubular junction and mid-ascending aorta. Mean growth rate 0.1—0.4 mm/yr. BAV associated with more rapid growth rate than TAV (0.44 ± 0.57 versus 0.18 ± 0.61 mm/yr/m²) |
| Mortensen 2013         | 102 | Eight locations in thoracic aorta at baseline, 2 yrs and 5 yrs | Significant growth seen in ascending but not descending aorta. Growth rates varied from 0.20 ± 0.34 to 0.38 ± 0.46 mm/yr for the three most proximal ascending aorta measurements. Age, CoA, BAV were associated with an accelerated growth while diastolic BP and hypertensive treatment were associated with slower growth | Significant growth seen in ascending but not descending aorta. Growth rates varied from 0.20 ± 0.34 to 0.38 ± 0.46 mm/yr for the three most proximal ascending aorta measurements. Age, CoA, BAV were associated with an accelerated growth while diastolic BP and hypertensive treatment were associated with slower growth |

(continued on next page)
the ascending aortic diameter. Using this measure, a ratio >1.5 is indicative of ascending aorta dilatation. However, this can be true only if the descending aorta diameter is normal. Another alternative, which correlates more closely with aortic diameter, is the use of the body surface area (BSA), and calculation of the ascending aortic size index (ASI) using the calculation: aortic diameter/BSA. The latter is more accurate in the assessment of aortic dilatation and the prediction of aortic dissection, with an ASI ≥2 cm/m² considered as aneurysmal, with a higher risk of future growth and/or dissection requiring close surveillance (an example is the patient shown in Fig 4), while an ASI ≥2.5 cm/m² poses an extremely high risk and a need for prompt surgical intervention.

Recently, Mortensen et al. have derived a mathematical model that uses current aortic dimensions, presence of BAV, aortic coarctation, diastolic blood pressure, and BSA to predict those with a high risk of rapid progression of aortic dilatation. However, this has yet to be externally validated in a prospective study.

MRI is inarguably the optimal method for assessment of the thoracic aorta. However, the precise choice of technique varies from centre to centre. A 2007 guideline on the management of TS suggested that the aorta should be measured in end-systole. This is readily achievable using a black blood turbo spin-echo (TSE) sequence, although this suffers from only measuring a single point of the aorta, and changes in slice angulation can lead to overestimation of diameter. Alternatively, a respiratory navigated, electrocardiogram (ECG)-gated three-dimensional (3D) steady-state free-progression (bSSFP) technique will provide images of the entire thoracic aorta in diastole, allowing accurate

Table 2 (continued)

| Study            | Age | Measurements      | Sequence | Findings |
|------------------|-----|-------------------|----------|----------|
| Carlson 2007 46  | 30-74| Echocardiography | n=20     | Twenty dissections in 22 yrs. Type A dissection in 85%, type B in 15%. Mean ASI = 2.7 ± 0.6 cm/m²; 95% spontaneous dissections had ABA, with 26% having an additional aortic pathology. Fourteen were 45-55, 25% had hypertensio. Annualised rate of 618/100,000 woman yrs. |
| Carlson 2007 46  | 30-74| MRI with black blood axial sequence at level of right pulmonary artery | n=15     | All had ASI >2.5. Dissection occurred in 25% with AD >3.5 cm, 33% of those with ASI >2.5, and only 3% with AD:DD >1.5. |
| Matura 2007 40  | 30-74| Echocardiography | n=15     | Annualised rate of 681/100,000 woman yrs. Twenty dissections in 22 yrs. Type A dissection in 85%, type B in 15%. Mean ASI was 2.7 ± 0.6 cm/m²; 95% spontaneous dissections had ABA, with 26% having an additional aortic pathology. Fourteen were 45-55, 25% had hypertensio. Annualised rate of 618/100,000 woman yrs. |
| Carlson 2007 46  | 30-74| MRI with black blood axial sequence at level of right pulmonary artery | n=10     | All had ASI >2.5. Dissection occurred in 25% with AD >3.5 cm, 33% of those with ASI >2.5, and only 3% with AD:DD >1.5. |
| Gravholt 2006 9  | 30-74| Echocardiography | n=10     | Fourteen were 45-55, 25% had hypertensio. Annualised rate of 681/100,000 woman yrs. Twenty dissections in 22 yrs. Type A dissection in 85%, type B in 15%. Mean ASI was 2.7 ± 0.6 cm/m²; 95% spontaneous dissections had ABA, with 26% having an additional aortic pathology. Fourteen were 45-55, 25% had hypertensio. Annualised rate of 618/100,000 woman yrs. |

* Same centre with overlapping populations.
* Included in Carlson literature review. Included separately as this is the only large-scale epidemiological review of dissection in TS.

Figure 4 An oblique coronal left ventricular outflow tract cine image (bSSFP) end diastolic frame of a 50-year-old patient with TS. Right top figure (white frame) shows a normal tricuspid aortic valve (white arrow) in this patient. Measurements of the annulus (A), sinus of Valsalva (SV), sinotubular junction (STJ), and ascending aorta (AA) were within the normal limits for an adult patient: 20, 27, 22, and 32 mm, respectively. However, the calculated ASI was 2.28 cm/m² (body surface area = 1.4 m²) indicating a higher risk of future growth and/or dissection.
measurement of the aortic root as well as the ascending and descending aorta, although this comes at a cost of a significantly prolonged acquisition time.\textsuperscript{45}

The data underpinning our understanding of aortic dissection in TS is extremely limited (Table 2). What is well established is that TS is associated with an elevated risk of developing aortic dissection and that dissections occur at a much earlier age. The incidence of aortic dissection is estimated to be as much as 100-fold higher in TS compared to the general population, although this value was based on only three dissections in a population of 166 females with TS.\textsuperscript{40} A more conservative estimate is a six-times increase in relative risk in a study by Gravholt et al.,\textsuperscript{9} although this compared the TS cohort with an unmatched population rate and is, therefore, likely extremely conservative. Most striking is the early age at which TS patients develop dissection, with a mean age of 30.5 years (interquartile range [IQR] 23.5–38.5), compared with a mean age in the general female population of 77 years.\textsuperscript{46} It is estimated that at least 1.4% of females with TS will suffer an aortic dissection.\textsuperscript{9}

One or more predisposing cardiovascular risk factors (BAV, aortic dilatation, and aortic coarctation) can be identified with cardiovascular imaging in up to 90% of aortic dissections in TS.\textsuperscript{9,13,15} Hypertension is also strongly associated with aortic dilatation and dissection, while upper extremity hypertension is a hallmark of significant aortic coarctation. However, aortic dilatation occurs at an early age in BAV and cannot thus be attributed solely to hypertension.\textsuperscript{47} Finally, pregnancy in TS appears to be associated with a high risk of dissection.\textsuperscript{48} In those who do dissect during pregnancy, prognosis is extremely poor with an 86% mortality in one series.\textsuperscript{49} Thus, careful cardiac and thoracic screening is essential in all those considering assisted contraception or pregnancy, with some experts advising an ASI >2 cm/m\textsuperscript{2} to be a contraindication to pregnancy.\textsuperscript{50}

Identification and intervention in high-risk individuals is challenging by the difficulty in defining a dilated aorta as mentioned before. In a study by Matura et al.,\textsuperscript{46} all patients with dissection had an ASI >2.5, while two-thirds had AD:DD >1.5. In a study by Carlson et al.,\textsuperscript{30} the mean ASI was 2.7 ± 0.6 cm/m\textsuperscript{2} in those with dissection, with two out of the 10 dissections occurring in patients with ASI <2.5 cm/m\textsuperscript{2}, although the measurements were with echocardiography and taken up to 6 years prior to the dissection. In a study cohort of 166 TS patients, it was shown that dissection occurred in 25% with AD >3.5 cm, 33% of those with ASI >2.5, and only 3% with AD:DD >1.5, suggesting ASI as the most useful indicator of a dilated aorta with requirement for urgent intervention when a threshold of 2.5 cm/m\textsuperscript{2} is reached. Although MRI is the technique of choice in the screening and follow-up of those at risk for dissection, computed tomography (CT) angiography is typically the technique of choice in the acute assessment of those presenting with symptoms of dissection due to its wide availability and speed. Ideally, CT aortography should be performed with ECG gating due to improved visualisation of the proximal ascending aorta.\textsuperscript{51}

Aortic coarctation affects 12% of women with TS.\textsuperscript{12} Additionally, elongated transverse arch and kinking of the isthmic portion of aorta can be seen in around half of all TS cases (Figs 5 and 6).\textsuperscript{12,52} This is likely part of a spectrum of abnormalities affecting the thoracic aorta, with elongated transverse arch as the mildest expression, and aortic arch hypoplasia/aplasia representing the most severe end of the spectrum, observed in around 2% of TS females.\textsuperscript{52} Aortic coarctation has been shown to be associated with dissection, and it has been proposed that elongated transverse arch may similarly predispose to dissection due to abnormal flow velocities and shear stress within the arch, although this has not been properly evaluated.\textsuperscript{12} Aortic coarctation is well evaluated with MRI, using either MR angiography (MRA) or a 3D bSSFP sequence, with both techniques showing a tight stenosis at the aortic isthmus with or without collateral formation. Current guidelines of the European Society of Cardiology suggest intervention when there is >50% stenosis at the coarctation compared to the aortic diameter at the diaphragm with hypertension (Class IIa recommendation) with consideration to intervene even in the absence of hypertension (Class IIb recommendation).\textsuperscript{53} Additional functional assessment can be performed with velocity-encoded cine-MRI. Indicators of significant flow impairment include: greater flow through the distal thoracic aorta than through the thoracic aorta immediately distal to the coarctation; retrograde intercostal artery flow; and a diastolic tail with loss of the normal systolic–diastolic variation in flow. A pressure gradient across the stenosis can be calculated using the modified Bernoulli equation ($\Delta P = 4v^2$) where $v$ is the maximum velocity through the coarctation. A gradient above 15 mmHg has been suggested as being significant on MRI, whereas echocardiography uses a threshold of 20 mmHg, which is similar to that used in invasive catheter measurements, although MRI often underestimates the peak velocity, hence the discrepancy.\textsuperscript{53,54} However, significant collateral flow can result in the pressure gradient being artificially low, which can result in the pressure gradient being artificially low.
Figure 6 Sagittal oblique cine SSFP image of a 55-year-old TS patient showing a high-riding aorta (white arrow), residual coarctation after surgical repair (white arrowhead), and dilatation of ascending aorta (white dashed arrow), with the ASI >2.5.

low, and thus, quantification of collateral flow is considered a more accurate assessment of the haemodynamic significance of the stenosis.55

Partial anomalous pulmonary venous return is the most common venous anomaly and is found in 13% of TS cases, compared with ~1% of the general population. This can present with right heart failure or pulmonary hypertension due to left to right shunting causing right ventricular and pulmonary volume overload.56 Careful scrutiny is important in cross-sectional imaging as visualisation of the pulmonary veins can be particularly challenging using transthoracic echocardiography.57,58 Persistent left-sided superior vena cava is also commonly found in TS (13%, compared to 1% in the general population). This is usually asymptomatic, but is important to report because it has the potential to cause confusion during central venous or right heart catheterisation, it may act as a route for paradoxical emboli when it inserts into the left atrium, and can cause complications in cardiothoracic surgery.59 A simple half-Fourier acquisition single-shot turbo spin-echo (HASTE) stack is often sufficient to visualise these anomalies. However, MRA or 3D bSSFP can also be useful to provide further visualisation of the vessels in case of uncertainty.

Other congenital cardiovascular disorders that can be observed in TS are ventricular septal defects, hypoplastic left heart syndrome, single ventricle, mitral valve abnormalities, atrial septal defects, coronary artery abnormalities, and aberrant right subclavian artery.14 In the retrospective review by Cramer et al.,16 two TS patients out of 173 had coronary artery abnormalities: one patient had an anomalous left coronary artery from the pulmonary artery, and the other patient had a small coronary artery fistula from the left coronary artery to the pulmonary artery. The risk for coronary artery disease is higher in TS women when compared to the general population.50 Women with TS more often have higher values of body mass index and waist:hip ratio, higher values of diastolic blood pressure, and higher levels of total cholesterol and low-density lipoprotein fraction, whereas levels of the high-density lipoprotein fraction are lower. Cardiac imaging in women with TS also reveals an increased left ventricular mass in association with aortic valve disease, age, hypertension, physical stature, and metabolic status.61,62

The imaging techniques

Transthoracic echocardiography is the imaging method of choice in the initial assessment of the cardiovascular system in the neonate, toddler, and young girl with TS. It provides an accurate and reliable non-irradiating assessment of the cardiovascular anatomy, including the root and the ascending part of the thoracic aorta and the entry of the pulmonary veins into the left atrium.32 However, in adolescents and adults, the shape of the thorax in TS can lead to suboptimal echocardiography images.39 In addition, transthoracic echocardiography is also limited in visualising the left upper pulmonary vein, and poor at visualisation of the thoracic aorta distal to the ascending portion.12,63,64 It has been generally accepted that a thorough characterisation of the cardiovascular anatomy is necessary at the time of TS diagnosis.58 Transthoracic echocardiography enables identification of the life-threatening cardiovascular disorders and their complications in the majority of children with TS. Although transthoracic echocardiography remains a standard follow-up investigation in many centres due to its availability and relatively low cost, in the case of incomplete or suboptimal visualisation of cardiovascular anatomy with echocardiography, or in the case of clinical indication, MRI should be performed.32,39 The importance of screening in younger age groups needs to be stressed because aortic dilatation can occur in girls as young as 5 years of age.13,63,66 At the age of 12 years, when most children would tolerate an MRI procedure without sedation, thoracic MRI should be performed.97 An imaging protocol has been previously proposed by Turtle et al.8 (Fig 7), which should be implemented at the transition to adulthood (around 16 years of age).

MRI provides an ionising radiation free and non-invasive assessment of cardiovascular anatomy with good visualisation of the heart chambers, myocardium, and the valves and a clear visualisation of the entire thoracic aorta, enabling recognition of the clinically and sonographically silent anomalies, such as a mild dilatation of the aorta or an elongation of the transverse aortic arch with kinking.12,39 As mentioned previously, MRI can supplement transthoracic echocardiography in cases of inadequate visualisation of the aortic valve leaflets and combination of both imaging methods yields diagnostic visualisation of the valve in almost all cases.22

In certain clinical conditions, there is a role for ECG-gated CT aortography in imaging of the acute aortic syndrome, and occasionally CT coronary angiography may be of use in the investigation of chest pain, particularly given the
Figure 7 A summary of recommended cardiovascular system imaging in patients with TS. (The grey highlighted section is adapted with permission from Turtle et al.*) (a) When aortic dissection and/or coarctation is clinically suspected. (b) When MRI is not available or contra-indicated. (c) When second transthoracic echocardiography is non-contributable. (d) When MRI can be without general sedation.
increased cardiovascular events in this population. ECG-gated CT angiography is the diagnostic method of choice in the setting of suspected aortic dissection in TS patients, clearly demonstrating the intimal flap, as well as the entry and re-entry sites and branch vessel involvement. This allows for prompt and accurate assessment on which to plan management strategies. Non-ECG-gated CT now allows for prompt and accurate assessment on which to plan and re-entry sites and branch vessel involvement. This allows for prompt and accurate assessment on which to plan management strategies. Non-ECG-gated CT

Discussion

A review of the literature on TS has demonstrated that cardiovascular disorders are a major factor in the higher SMR of these patients compared to the general population. More troublesome is the early age at which TS patients can develop life-threatening cardiovascular complications. It is generally accepted that at the time of diagnosis of TS, echocardiography should be routinely performed as a part of a full cardiovascular evaluation. The review also demonstrates that thorough imaging of the aortic valve and the thoracic aorta are essential. Although, the specific timing of screening and follow-up are as yet undetermined, Fig 7 summarises our recommendations for a long-term cardiovascular imaging programme for patients with TS.

Conclusion

Turner's syndrome is associated with high mortality from cardiovascular disorders. Awareness of the common findings in Turner's, in combination with a structured approach to imaging and follow-up, will provide maximum yield in terms of early identification and management of a wide range of potentially serious cardiovascular conditions.

Acknowledgements

J.R. Weir-McCall is supported by the Wellcome Trust through the Scottish Translational Medicine and Therapeutics Initiative (Grant no. WT 085664) in the form of a Clinical Research Fellowship.

References

1. Nielsen J, Wohlert M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Aarhus, Denmark. Birth Defects Orig Artic Ser 1990;26:209–23. http://dx.doi.org/10.1007/978-1-4684-0215-0.57.

2. Stochholm K, Juul S, Juel K, et al. Prevalence, incidence, diagnostic delay, and mortality in Turner's syndrome. J Clin Endocrinol Metab 2006;91(10):3897–902. http://dx.doi.org/10.1210/jc.2006-0558.

3. Schoemaker MJ, Swedlow AJ, Higgs CD, et al. Mortality in women with Turner's syndrome in Great Britain: a national cohort study. J Clin Endocrinol Metab 2008;93(12):4733–42. http://dx.doi.org/10.1210/jc.2008-1049.

4. Sybert VP, McCauley E. Turner's syndrome. N Engl J Med 2004;351(12):1227–38. http://dx.doi.org/10.1056/NEJMra030360.

5. Bondy CA. Congenital cardiovascular disease in Turner's syndrome. Congenit Heart Dis 2008;3(1):2–15. http://dx.doi.org/10.1111/j.1747-0803.2007.00163.x.

6. Barr M, Oman-Ganes L. Turner's syndrome morphology and morphometrics: cardiac hypoplasia as a cause of midgestation death. Teratology 2002;66(2):65–72. http://dx.doi.org/10.1002/tera.10064.

7. Sybert VP. Cardiovascular malformations and complications in Turner's syndrome. Pediatrics 1998;101(1):E11. http://dx.doi.org/10.1542/peds.101.1.e11.

8. Turtle EJ, Sule AA, Bath LE, et al. Assessing and addressing cardiovascular risk in adults with Turner's syndrome. Clin Endocrinol (Oxf) 2013;78(5):639–45. http://dx.doi.org/10.1111/cen.12104.

9. Gravholt CH, Landin-Wilhelmsen K, Stochholm K, et al. Clinical and epidemiological description of aortic dissection in Turner's syndrome. Cardiol Young 2006;16(5):430–6. http://dx.doi.org/10.1017/S1047951106000928.

10. Bolar K, Hoffman AR, Maneatis T, et al. Long-term safety of recombinant human growth hormone in Turner's syndrome. J Clin Endocrinol Metab 2008;93(2):344–51. http://dx.doi.org/10.1210/jc.2007-1723.

11. Sakakibara H, Yoshida H, Takei M, et al. Health management of adults with Turner's syndrome: an attempt at multidisciplinary medical care by gynecologists in cooperation with specialists from other fields. J Obstet Gynaecol Res 2011;37:836–42. http://dx.doi.org/10.1111/j.1447-0756.2010.01448.x.

12. Ho VB, Bakalov VK, Cooley M, et al. Major vascular anomalies in Turner's syndrome: prevalence and magnetic resonance angiographic features. Circulation 2004;110:1694–700. http://dx.doi.org/10.1161/01.CIR.0000142290.35842.B0.

13. Lin AE, Lippe B, Rosenfeld RG. Further delineation of aortic dilation, dissection, and rupture in patients with Turner's syndrome. Pediatrics 1998;102(1):e12. http://dx.doi.org/10.1542/peds.102.1.e12.

14. Cramer JW, Bartz P, Simpson PM, et al. The spectrum of congenital heart disease and outcomes after surgical repair among children with Turner's syndrome: a single-center review. Pediatr Cardiol 2014;35(2):253–60. http://dx.doi.org/10.1007/s00246-013-0766-5.

15. Elsheikh M, Casadei B, Conway GS, et al. Hypertension is a major risk factor for aortic root dilatation in women with Turner's syndrome. Clin Endocrinol (Oxf) 2001;54:69–73. http://dx.doi.org/10.1046/j.1365-2265.2001.01154.x.

16. Clark EB. Neck web and congenital heart defects: a pathogenic association in 45 X-O Turner's syndrome? Teratology 1984;29:355–61.

17. Loscalzo ML, Van PL, Ho VB, et al. Association between fetal lymphedema and congenital cardiovascular defects in Turner's syndrome. Pediatrics 2005;115:732–5. http://dx.doi.org/10.1542/peds.2004-1369.

18. Bondy C, Bakalov VK, Cheng C, et al. Bicuspid aortic valve and aortic coarctation are linked to deletion of the X chromosome short arm in Turner's syndrome. J Med Genet 2013;50(10):662–5. http://dx.doi.org/10.1136/jmedgenet-2013-101720.

19. Miyaibara S, Nakayama M, Suzumori K, et al. Developmental analysis of cardiovascular system of 45,X fetuses with cystic hygroma. Am J Med Genet 1997;68:135–41. http://dx.doi.org/10.1002/(SICI)1098-8628(19970120)68:2<135::AID-AJMG3>3.0.CO;2-D.

20. Gravholt CH, Juul S, Naeraa RW, et al. Morbidity in Turner's syndrome. J Clin Epidemiol 1998;51(2):147–58. http://dx.doi.org/10.1016/S0895-4356(97)00237-0.

21. Brauerman AC, Guven H, Beardse MA, et al. The bicuspid aortic valve. Curr Prob Cardiol 2005;30:470–522. http://dx.doi.org/10.1016/j.cpcardiol.2005.06.002.

22. Sachdev V, Matura LA, Sidenko S, et al. Aortic valve disease in Turner's syndrome. J Am Coll Cardiol 2008;51(19):1904–9. http://dx.doi.org/10.1016/j.jacc.2008.02.035.
23. Rossi A, Van Der Linde D, Yap SC, et al. Ascending aorta dilatation in patients with bicuspid aortic valve stenosis: a prospective CMR study. Eur Radiol 2013;23(3):642–9. http://dx.doi.org/10.1007/s00330-012-2651-2.

24. Mortensen KH, Hjerrild BE, Stochholm K, et al. Dilation of the ascending aorta in Turner’s syndrome—a prospective cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2011;13(1):24. http://dx.doi.org/10.1186/1532-429X-13-24.

25. Van Engelen K, Bartelings MM, Gittenberger-De Groot AC, et al. Bicuspid aortic valve morphology and associated cardiovascular abnormalities in fetal Turner’s syndrome: a pathomorphological study. Fetal Diagn Ther 2014;36:59–68. http://dx.doi.org/10.1159/000357706.

26. Fernandes SM, Sanders SP, Khairy P, et al. Morphology of bicuspid aortic valve in children and adolescents. J Am Coll Cardiol 2004;44:1648–51. http://dx.doi.org/10.1016/j.jacc.2004.05.063.

27. Russo CF, Cannata A, Lanfranchi M, et al. Is aortic wall degeneration related to bicuspid aortic valve anatomy in patients with valvular disease? J Thorac Cardiovasc Surg 2008;136:937–42. http://dx.doi.org/10.1016/j.jtcvs.2007.11.072.

28. Bonow RO. Bicuspid aortic valves and dilated aortas: a critical review of the ACC/AHA practice guidelines recommendations. Am J Cardiol 2008;102(1):111–6. http://dx.doi.org/10.1016/j.amjcard.2008.01.058.

29. Hope MD, Hope TA, Brook SE, et al. 4D flow CMR in assessment of valve-related ascending aortic disease. JACC Cardiovasc Imaging 2011;4(7):781–7. http://dx.doi.org/10.1016/j.jcmg.2011.05.004.

30. Hope MD, Hope TA, Meadows AK, et al. Bicuspid aortic valve: four-dimensional MR evaluation of ascending aortic systolic flow patterns. Radiology 2010;255(1):53–61. http://dx.doi.org/10.1148/radiol.09091437.

31. Mahadeva R, Barker AJ, Schaefer M, et al. Bicuspid aortic cusp fusion morphology alters aortic three-dimensional outflow patterns, wall shear stress, and expression of aortopathy. Circulation 2014;129:673–82. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.003026.

32. Lanzarini L, Larizza D, Prete G, et al. Aortic dimensions in Turner’s syndrome: two-dimensional echocardiography versus magnetic resonance imaging. J Cardiovasc Med (Hagerstown) 2007;8(6):428–37. http://dx.doi.org/10.1093/109055/00006791.

33. Alegret JM, Palazon O, Duran I, et al. Aortic valve morphology definition with transthoracic combined with transesophageal echocardiography in a population with high prevalence of bicuspid aortic valve. Int J Cardiovasc Imaging 2005;21(2–3):213–7. http://dx.doi.org/10.1007/s10554-004-3901-9.

34. Chan KL, Stinson WA, Veinot JP. Reliability of transthoracic echocardiography in the assessment of aortic valve morphology: pathological correlation in 178 patients. Can J Cardiol 1999;15(1):48–52.

35. Ayad RF, Grayburn PA, Ko JM, et al. Accuracy of two-dimensional echocardiography in determining aortic valve structure in patients >50 years of age with bicuspid aortic valve replacement for aortic stenosis. Am J Cardiol 2011;108(1):1589–90. http://dx.doi.org/10.1016/j.amjcard.2011.09.006.

36. Garcia J, Kadem L, Larose E, et al. Comparison between cardiovascular magnetic resonance and transthoracic Doppler echocardiography for the estimation of effective orifice area in aortic stenosis. J Cardiovasc Magn Reson 2011;13:25. http://dx.doi.org/10.1186/1532-429X-13-25.

37. Garcia J, Capoulade R, Le Vien F, et al. Discrepancies between cardiovascular magnetic resonance and Doppler echocardiography in the measurement of transvalvular gradient in aortic stenosis: the effect of flow vorticity. J Cardiovasc Magn Reson 2013;15:84. http://dx.doi.org/10.1186/1532-429X-15-84.

38. Cawley PJ, Hamilton-Craig C, Owens DS, et al. Prospective comparison of valve regurgitation-quantification by cardiac magnetic resonance imaging and transthoracic echocardiography. Circ Cardiovasc Imaging 2013;6(1):48–53. http://dx.doi.org/10.1161/CIRCIMAGING.112.975623.

39. Hjerrild BE, Mortensen KH, Andersen NH, et al. Prediction of aortic dilatation in Turner’s syndrome: enhancing the use of serial cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2013;15:47. http://dx.doi.org/10.1186/1532-429X-15-47.

40. Wolak A, Gransar H, Thompson LE, et al. Aortic size assessment by contrast computed tomography: normal limits by age, gender, and body surface area. JACC Cardiovasc Imaging 2008;1:200–9. http://dx.doi.org/10.1016/j.jcmg.2007.11.005.

41. Hjerrild BE, Mortensen KH, Sørensen KE, et al. Thoracic aortopathy in Turner’s syndrome and the in vivo vorticity. J Cardiovasc Magn Reson 2011;13(1):24. http://dx.doi.org/10.1186/1532-429X-13-24.

42. Roman MJ, Devereux RB, Kramer-Fox R, et al. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 1989;64:507–12. http://dx.doi.org/10.1016/0002-9149(89)90430-X.

43. Cawley PJ, Hamilton-Craig C, Owens DS, et al. Recommendations for the diagnosis and management of Turner’s syndrome. J Clin Endocrinol Metab 2001;86(7):3061–9. http://dx.doi.org/10.1210/jcem.86.7.7683.
59. Povoski SP, Khabiri H. Persistent left superior vena cava: review of the literature, clinical implications, and relevance of alterations in thoracic central venous anatomy as pertaining to the general principles of central venous access device placement and venography in cancer. World J Surg Oncol 2011;9(1):173. http://dx.doi.org/10.1186/1477-7819-9-173.

60. Kozłowska-Wojciechowska M, Jeż W, Zdrojewski T, et al. Are young women with Turner’s syndrome at greater risk of coronary artery disease? Eur J Cardiovasc Prev Rehabil 2006;13(3):467–9.

61. Mortensen KH, Gravholt CH, Hjerrild BE, et al. Left ventricular hypertrophy in Turner’s syndrome: a prospective echocardiographic study. Echocardiography 2012;29(9):1022–30. http://dx.doi.org/10.1111/j.1540-8175.2012.01754.x.

62. Tancredi G, Versacci P, Pasquino AM, et al. Cardiopulmonary response to exercise and cardiac assessment in patients with Turner’s syndrome. Am J Cardiol 2011;107(7):1076–82. http://dx.doi.org/10.1016/j.amjcard.2010.11.035.

63. Gutmark-Little I, Backeljauw PF. Cardiac magnetic resonance imaging in Turner’s syndrome. Clin Endocrinol (Oxf) 2013;78(5):646–58. http://dx.doi.org/10.1111/cen.12157.

64. Huang X, Huang Y, Huang T, et al. Individual pulmonary vein imaging by transthoracic echocardiography: an inadequate traditional interpretation. Eur J Echocardiogr 2008;9(5):655–60. http://dx.doi.org/10.1093/ejechocard/jen132.

65. Chalard F, Ferey S, Teinturier C, et al. Aortic dilatation in Turner’s syndrome: the role of MRI in early recognition. Pediatr Radiol 2005;35(3):323–6. http://dx.doi.org/10.1007/s00247-004-1359-5.

66. Sharma J, Friedman D, Dave-Sharma S, et al. Aortic distensibility and dilatation in Turner’s syndrome. Cardiol Young 2009;19(6):568–72. http://dx.doi.org/10.1017/S104795110990874.

67. McCarthy K, Bondy CA. Turner’s syndrome in childhood and adolescence. Expert Rev Endocrinol Metab 2008;3:771–5. http://dx.doi.org/10.1586/17446651.3.6.771.

68. Lee SH, Jung JM, Song MS, et al. Evaluation of cardiovascular anomalies in patients with asymptomatic Turner’s syndrome using multidetector computed tomography. J Korean Med Sci 2013;28(8):1169–73. http://dx.doi.org/10.3346/jkms.2013.28.8.1169.

69. Getzschke CO, Krag-Olsen B, Nielsen J, et al. Prevalence of cardiovascular malformations and association with karyotypes in Turner’s syndrome. Arch Dis Child 1994;71:433–6. http://dx.doi.org/10.1136/adc.71.5.433.

70. Davies MC, Culekli R, Jacobs HS. Osteoporosis in Turner’s syndrome and other forms of primary amenorrhea. Clin Endocrinol (Oxf) 1995;43(6):741–6.

71. Landin-Wilhelmsen K, Bryman I, Windh M, et al. Osteoporosis and fractures in Turner’s syndrome—importance of growth promoting and osteogen therapy. Clin Endocrinol (Oxf) 1999;51(4):497–502.

72. Bakalov VK, Chen ML, Baron J, et al. Bone mineral density and fractures in Turner’s syndrome. Am J Med 2003;115(4):259–64. http://dx.doi.org/10.1016/S0002-9343(03)00364-4.

73. Pinsker JE. Clinical review: Turner’s syndrome: updating the paradigm of clinical care. J Clin Endocrinol Metab 2012;97(6):E994–1003. http://dx.doi.org/10.1210/jc.2012-1245.

74. Trzcinska D, Olaszewska E, Wiśniewski A, et al. The knee alignment and the foot arch in patients with Turner’s syndrome. Pediatr Endocrinol Diabetes Metab 2011;7:138–44.

75. Lippe B, Geffner ME, Dietrich RB, et al. Renal malformations in patients with Turner’s syndrome: imaging in 141 patients. Pediatrics 1988;82(6):852–8.

76. Bilge I, Kayserili H, Emre S, et al. Frequency of renal malformations in Turner’s syndrome: analysis of 82 Turkish children. Pediatr Nephrol 2000;14(12):1111–4.

77. Dawson-Falk KI, Wright AM, Bakker B, et al. Cardiovascular evaluation in Turner’s syndrome: utility of MR imaging. Australas Radiol 1992;36(3):204–9.

78. Castro AVB de, Okoshi K, Ribeiro SM, et al. Cardiovascular assessment of patients with Ullrich–Turner syndrome on Doppler echocardiography and magnetic resonance imaging. Arq Bras Cardioi 2002;78(1):51–8.

79. Ilyas M, Chu C, Ettles D, et al. Evaluation by magnetic resonance imaging of aortic dilatation and coarctation in adult Turner’s syndrome patients. Clin Endocrinol (Oxf) 2006;65(2):154–7. http://dx.doi.org/10.1111/j.1365-2265.2006.02355.x.

80. Bondy CA, Van PL, Bakalov VK, et al. Growth hormone treatment and aortic dimensions in Turner’s syndrome. J Clin Endocrinol Metab 2006;91(5):1785–8. http://dx.doi.org/10.1210/jc.2005-2625.

81. Cleemann L, Mortensen KH, Holm K, et al. Aortic dimensions in girls and young women with Turner’s syndrome: a magnetic resonance imaging study. Pediatr Cardiol 2010;31(4):497–504. http://dx.doi.org/10.1007/s00246-009-9626-8.

82. Kim HK, Gottliebson W, Hor K, et al. Cardiovascular anomalies in Turner’s syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young adult population. AJR Am J Roentgenol 2011;196(2):454–60. http://dx.doi.org/10.2214/AJR.10.4973.