International Congress Series 1298 (2006) 123 – 130

www.ics-elsevier.com

Monitoring of congenital heart disease (CHD) and aortic dilatation in Turner syndrome: Italian experience

L. Mazzanti [a,*], D. Prandstraller [b], R. Fattori [c], L. Lovato [c], A. Cicognani [a], Italian Study Group for Turner Syndrome (ISGTS) [1]

[a] *Department of Pediatrics, University of Bologna, S.Orsola-Malpighi Hospital, Bologna, Italy*
[b] *Department of Cardiology and Cardio-Surgery of Development, University of Bologna, S.Orsola-Malpighi Hospital, Bologna, Italy*
[c] *Department of Radiology, University of Bologna, S.Orsola-Malpighi Hospital, Bologna, Italy*

Abstract. Subjects with X-monosomy are at high risk for cardiovascular diseases in particular CHD. Recent data reports an association with a generalized vasculopathy in particular aortic abnormalities such as dilatation and dissection. In fetal life there are typical signs of lymphatic obstruction that have been connected pathogenetically with CHD. In postnatal life characteristic dysmorphic signs, such as webbed neck, and karyotype distribution have to be considered risk factors for severe CHD and also for aortic dilatation (AoDil). We could evaluate this relationship in a large group of TS subjects enrolled in the study conducted by the Italian Study Group for Turner Syndrome (ISGTS). For the subjects with severe dysmorphic signs, the relative risk of CHD is higher than for the subjects with minor or moderate stigmata: in particular partial anomalous pulmonary vein drainage (PPAVD), coarctation of the aorta (COA) and also bicuspid aortic valve (BAV). The 45,X and Y-mosaicism subjects had a significantly higher prevalence of CHD (COA and PPAVD) than

* Corresponding author. Pediatric Clinic, University of Bologna, Via Massarenti 11, 40138-Bologna, Italy. Tel.: +39 051 6363643 (hospital); fax: +39 051 63634440.
E-mail address: laura.mazzanti@unibo.it (L. Mazzanti).

[1] Participating investigators: The Italian Study Group for Turner Syndrome (ISGTS): Rosalba Bergamaschi, MD, Emanuela Scarano, MD (Bologna), Franco Rigon, MD, Anna Licursi, MD (Padova), Daniela Larizza, MD (Pavia), Anna Maria Pasquino, Ida Pucarelli, MD (Roma), Giuseppe Chiumello, Maria Pia Guarneri (Milano), Francesco Prisco (Napoli), Francesco De Luca, MD (Messina), Roberto Salti, MD (Firenze), Alba Pilotta, MD (Brescia), Patrizia Matarazzo, MD (Torino), Giorgio Radetti, MD (Bolzano), Maria Carlotta Ragusa, MD (Catania), Sergio Bernasconi, MD (Parma), Luciano Tato', MD (Verona), Maddalena Sposito, MD (Perugia), Vincenzo De Sanctis, MD (Ferrara), Teresa Gentile, MD (L'Aquila), Giorgio Tonini, MD (Trieste), Vittorio Pullano (Catanzaro), Gianni Bona (Novara).

doi:10.1016/j.ics.2006.06.013

the other karyotype groups. AoDil has a higher prevalence than in the general population. In a series of 181 subjects followed-up in our clinic, we evaluated the prevalence and the follow-up of AoDil. High aortic dimensions indexed to body surface area were found in 24.1% of the subjects and in 37.8% of those with CHD. All the CHD involving the aorta increased the risk of AoDil: in particular 50% of subjects with COA had AoDil. AoDil was associated with a severe phenotype and 45.6% of subjects with severe stigmata had AoDil. In 49 of these subjects, without CHD echo and MRI were compared in the study of the aorta. At echocardiografic evaluation, a higher prevalence of indexed values above the upper normal limits was found than at MRI, in particular at ascending aorta. We think that the echo approach may cause some distortion in the image of the thoracic aorta in these subjects. In conclusion: TS should receive a complete cardiac evaluation and follow-up for CHD and also without CHD for aortic dilation, and blood pressure. A severe phenotype has to be considered a risk factor for CHD and AoDil. We emphasize the importance of MRI to detect better aortic dilation in all the patients between 15 and 20 years of age.

Keywords: Congenital heart disease; Karyotype; Turner stigmata; Aortic dilatation; Aortic MRI

1. CHD and prenatal life

In fetal life, there are typical obstetric ultrasonographic findings associated with TS: increased nuchal translucency at 11–14-week scan, cystic hygroma and fetal hydrops up to 21 weeks of gestational age. These signs are accompanied by a high rate of CHD and spontaneous fetal loss (80–90%). A pathogenetic connection between fetal lymphatic obstruction and CHD has been demonstrated. In fact in postnatal life characteristic dysmorphic features such as webbed neck have to be considered as risk factors for severe CHD [1–4]. The prenatal distribution by karyotype is generally 45,X in more than 90% of the cases with only a small proportion of mosaics. Prenatally, the incidence of CHD is higher than postnatally (60% vs. 20–30%) [1] and also CHD distribution is different: COA is the most prevalent (45%) followed by hypoplastic left heart syndrome (HLHS—13%). Gunther et al. [5] presented interesting data about the different CHD prevalence in two groups of patients with Turner syndrome traditionally diagnosed by villocentesis or amniocentesis (when there was an US sign of suspicion) or incidentally (with routine procedure). The group incidentally diagnosed had a higher prevalence of mosaicism, but a significantly lower prevalence of CHD than the traditional group (30% towards 64%), the same as in postnatal life.

2. CHD and postnatal life

2.1. Prevalence of CHD

In accordance with the different studies the prevalence of CHD was between 23% and 40% versus 2% of the general population (GP) [3,6–9]. The relative risk (RR) of CHD was 11–19 times higher in TS than in the GP. In echocardiographic studies, the left-sided obstructive defects predominate: BAV, COA and aortic valve disease (AoVD).

We had the possibility to update our previous study conducted in Italy by the Italian Study Group for Turner Syndrome (ISGTS) [3]. Six hundred and eighty-two unselected subjects were enrolled. At the first evaluation, their mean chronological age was 10.7±5.7 years

(1 month–30 years) and at the last observation their age was between 3 and 35.7 years of age. CHD prevalence was of 22.6%. Associated defects were very frequent and were found in 22% of the CHD patients. PAPVD had the highest RR (320 times more than in the GP) as reported by other authors [3,8,10–13]. Frequently, in these subjects, PAPVD appears in isolation different than the GP. Aberrant pulmonary veins are found more frequently on the left side than in the GP where the right side is the most frequently involved.

2.2. Karyotype, Turner stigmata and CHD

Karyotype and characteristic dysmporphic features have to be considered for the risk of severe CHD in TS. Our updated study permitted us to evaluate this relationship better.

45,X and Y-mosaicism subjects had a significantly higher prevalence of CHD (29.3% and 31.3%, respectively) than the other karyotype groups (X-mosaicism: 25%–X-structural abnormalities: 9.3%; $X^2=30.15$, $p=0.00001$). The subjects with Y-mosaicism had a RR of ventricular septal defect (VSD) 6.9 times (95% CI: 4.4–10.8) higher than 45,X subjects (Fig. 1).

In our study, 576 of the 682 subjects with TS were evaluated also for dysmorphic external features (Turner stigmata) that were classified into three subgroups: minor, moderate or severe. 32% of them had severe Turner stigmata with a different distribution by karyotype: 68.4% for 45,X patients, 15.8% Y-chromosome mosaicism, 10.5% X-structural abnormalities (X-SA) and 5.3% X-mosaicism ($X^2=50.09$, $p=0.0001$).

The patients with webbed neck had a higher risk of CHD than the patients without, in particular of COA: RR: 2.53 (95% CI: 1.7–3.2) ($X^2=27.7$, $p=0.000001$). 45,X subjects with severe dysmorphic features had a higher prevalence of severe CHD (COA and PAPVD) than the other karyotype groups ($X^2=56.7$, $p=0.000001$).

The subjects with severe Turner stigmata had a higher prevalence and higher RR than the patients with minor or moderate stigmata of CHD (RR=2.7, 95% CI: 1.6–4.6) ($X^2=14.2$, $p=0.0001$), PAPVD (RR=15.6, 95% CI: 3.5–68.8) ($X^2=24.3$, $p=0.000001$), COA (RR=2.4, 95% CI: 1.2–4.9) ($X^2=6.6$, $p=0.01$) and BAV (RR=2.2, 95% CI: 1.3–3.5) ($X^2=9.9$, $p=0.001$).

The individuals with severe Turner stigmata had a higher RR also of aortic dilatation (RR=1.8, 95% CI: 1.1–2.8) ($X^2=6.7$, $p=0.009$).

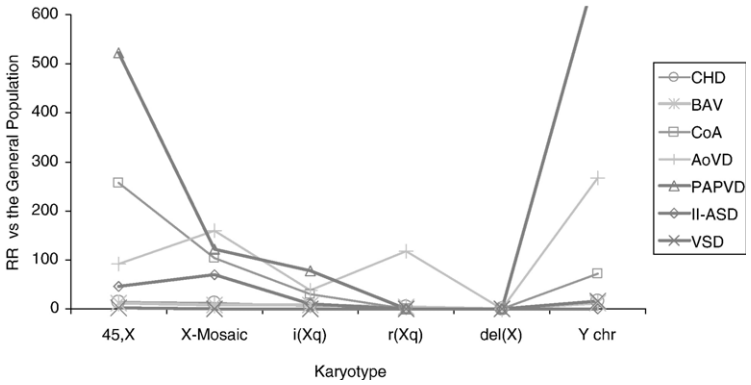

Fig. 1. Relative risk of CHD in TS in the different karyotypes compared with the general population.

3. Aortic dilatation

Recent data reports an association between TS subjects and generalized vasculopathy in particular aortic abnormalities such as dilatation or dissection [7,14–19]. AoDil has a higher prevalence than in the GP and involves aortic root, ascending aorta, occasionally extending to the aortic arch and the descending aorta. The prevalence of aortic dilatation was different according to the different studies: 8%—Lin et al. [15], 3.8%—Mazzanti and Cacciari [3], 42%—Elsheikh et al. [17], 5%—Chalard et al. [20] and 16%—Ostberg et al. [21].

In our study performed on 181 unselected individuals with TS followed-up in our clinic for a long time 5.8–25.6 years with full cardiologic evaluation, we evaluated the prevalence and the follow-up of AoDil and the possible influencing factors such as karyotype, severe Turner stigmata and GH and estrogen therapies.

3.1. Subjects

At the first examination, their mean chronological age was 10.8 + 6.0 years (1 month–35.7 years) and at the last one the age was between 3 and 45 years (mean 18.4 ± 10.3 years). The follow-up was of 9.5 ± 7 years (6–25.6 years). Karyotype distribution was: 45,X (42%), X-SA (34.8%), X-mosaicism (15.6%) and Y-mosaicism (7.6%). Severe Turner stigmata were found in 57 of 178 patients (32%).

3.2. Methods

Aorta dimensions were evaluated according to standard criteria at anulus, sinuses of valsalva, sinotubular junction, ascending aorta and aortic arch (Lang, 2005). We considered as normal the values included in the 95% normal confidence limits indexed to body surface area [22,23]: upper normal limits of aortic root dimensions at sinuses of valsalva = 2.1 (cm/m^2), at supraaortic ridge = 1.9 (cm/m^2) and at proximal ascending aorta = 1.9 (cm/m^2).

3.3. Results

In our series, CHD prevalence was of 18.8%. At echocardiographic evaluation, 24.1% of our patients showed AoDil. 37.8% of the individuals with CHD had AoDil: 50% of the subjects with COA showed AoDil, 33.3% of the subjects with AoVD and 34.4% of the subjects with BAV. AoDil was associated with a severe phenotype: 45.6 of patients with severe stigmata had AoDil. The individuals with severe phenotypic stigmata had a RR 1.9 times more than those with less severe stigmata. At multiple regression analysis, we considered many factors that could influence AoDil in TS: excluding age influence, a severe phenotype showed a positive influence on AoDil ($p = 0.05$), instead estrogens showed a negative one ($p = 0.007$) (protective effect?); GH therapy and karyotype had no influence on AoDil.

3.4. Conclusions

In our series of TS individuals, the prevalence of AoDil was of 24.1% at echo. The prevalence that we found was high and it was high also in young subjects. For AoDil, there

is no data of comparison with the GP, but in any case in younger women this event is extremely rare.

It has been reported that most patients with AoDil have an associated risk factor, such as BAV or COA or high blood pressure (HBP). In our series, the subjects with CHD showed a higher RR of AoDil than the subjects without, 4.8 times more ($X^2=9.1$, $p=0.002$). The risk of AoDil was high in particular in the most severe CHD such as COA in isolation or associated with PPAVD. In any case, all the CHD involving the aorta (AoVD and BAV) increased the risk of AoDil as happens in the GP.

In our series, the follow-up did not show any progressive or rapid evolution at this age and no BAV evolved towards AoVD. We found AoDil also in individuals with no risk factors. A longer follow-up until an older age is mandatory.

Concerning aortic dissection only one of the 682 subjects enrolled in the study of the ISGTS had high blood pressure, treated with β-blocker therapy, but no CHD or aortic dilation, and died at 20 years and 10 months of age for aortic dissection. The histologic specimen showed cystic medial necrosis of the aortic wall [24].

4. Aortic dilatation, comparison of echo and MRI in subjects without CHD

In the literature, there is little data on the prevalence and natural history of AoDil during adolescence and young adult age [20,24–26]. In particular, no prevalence data have been reported in subjects without CHD at this young age. Echocardiografic evaluation is widely available but has limiting factors such as chest wall anomalies and suboptimal alignement of cardiac structures. Thoracic MRI permits clear imaging and reveals unsuspected anomalies [18,21]. The aim of our study was to evaluate AoDil prevalence at echocardiography and MRI in patients without CHD aged over 15 years, followed for at least 5 years.

4.1. Subjects

Forty-nine of our subjects without CHD and age over 15 years (15–35.2 years) had a cardiologic re-evaluation with echo (2D and color Doppler) and transthoracic MRI. Their karyotype distribution was: 45,X: 24 pts (45%), X-mosaicism: 9 pts (17%), X-SA: 20 pts (38%).

4.2. Methods

At transthoracic MRI (fast black-blood T_1-weighted spin-echo), aortic diameters were evaluated using the same criteria as for echo [22]. Maximal ascending aortic diameter was measured in the axial slice.

4.3. Results

At sinuses of valsalva MRI showed a prevalence of AoDil (within and above upper normal limits) of 16% (8/49) and at proximal ascending aorta of 20.4% (10/49). At MRI, 14 individuals showed AoDil (14/49—28.6%) and 5 of them had values above upper normal limits (5/49—10.2%) (see Table 1).

At sinuses of valsalva echo showed a prevalence of AoDil (within and above upper normal limits) of 20.4% (10/49) and at proximal ascending aorta of 30.6% (15/49). At echo, 18 subjects showed AoDil (18/49—36.7%) and 11 of them were above upper normal limits (11/49—22.4%) (see Table 1).

Echo showed a higher prevalence of subjects with AoDil at proximal ascending aorta (30.6% vs. 20.4% of MRI) and of AoDil above upper normal limits than MRI (11 vs. 5 subjects; 22.4% and 10.2%, respectively).

There was no difference in the prevalence of AoDil in the various karyotype groups.

4.4. Conclusions

This data confirms the higher prevalence of AoDil in TS subjects than in the GP also for AoDil above the upper normal limits. Echo approach may cause some distortion in the image of the thoracic aorta in these subjects and this may explain the higher AoDil prevalence found at echo than at MRI in the proximal ascending aorta. As previously reported [18,20,25,26], we think that the importance of aorta MRI should be enmphasized in the cardiovascular evaluation of patients with Turner syndrome, in particular when an ascending AoDil is detected at echo and in any case before seeking to become pregnant.

5. Recommendations at diagnosis

5.1. Prenatal life

In prenatal life, the detection of CHD is with fetal morphological echography at 20–21 weeks of gestation and a second fetal echography at 32 weeks.

5.2. Postnatal life

Patients with echocardiography in the prenatal or newborn period need a complete cardiac examination after 1 month of life by a paediatric cardiologist.

At diagnosis at whatever age, it has been made patients need a complete cardiac examination (ECG, echocardiogram, BP) by a cardiologist with experience of GUCH to exclude BAV or COA.

Table 1
Aortic dilatation prevalence at echo and MRI in 49 subjects without CH considering indexed values above upper normal limits

Aortic dilatation	ECHO—subjects no. (%)	MRI—subjects no. (%)
Aortic root (sinuses of valsalva)	4 (8.2%)	3 (6.1%)
Ascending aorta	10 (20.4%)	5 (10.2%)
Ao root+ascending Ao	3	3
Aortic arch	0	0
Descending aorta	0	0

95% normal confidence limits indexed to body surface area [22].

6. Recommendations at follow-up

6.1. Follow-up of patients without CHD

For patients with TS even without CHD, a long-term follow-up is required to evaluate AoDil that may develop later. Physical examination at least once a year (BP, heart auscultation, peripheral pulses)

- After 10 years of age (*at 5-year intervals*): complete cardiac examination (cardiologist with experience of GUCH) with ECG, BP, echocardiography (in particular aortic root and systolic left ventricle function).
- At adolescence, young adult age and adulthood: accurate determination of aortic valve is very important: aortic dimension, the development of AS, AI and particular attention paid to the systolic left ventricle function.

When the thoracic window is acceptable, the echocardiographic evaluation should be performed by a skilled cardiologist. A close working relationship with a cardiologist with knowledge of TS is of great value.

The follow-up of AoDil should be performed with echo and the periodicity of evaluation will depend on aortic dimension and function.

Routine echo is not sufficient, when the thoracic window is poor.

At adolescence, a thoracic cardiovascular MR should be performed:

- to have a clear imaging of all the great vessels: aortic anulus, ascending aorta, aortic arch, descending aorta;
- to reveal unsuspected extra-cardiac vascular anomalies (PPAVD of only one pulmonary vein, LSVC, elongation of the transverse aortic arch);
- to permit a functional study of the aortic wall (aortic compliance).

The individuals that need MRI evaluation (high risk group) are those with COA, BAV, AoDil at echo, with a poor chest window and to decide for assisted reproduction.

6.2. Follow-up of patients with CHD

Patients with CHD require long-term cardiological follow-up. The cardiologist should decide the periodicity of evaluations.

HLHS: Hypoplastic left heart syndrome is rarely described, it leads to early death if untreated.

COA: Surgical repair before the first year of life is less likely to be associated with persistent hypertension (4.2% vs. 27%) [27]. There are indirect signs to be researched: left ventricle hypertrophy and possible associated anomalies. Aortic hystmus has to be visualized at echography and Doppler. Continuous Doppler curve analysis is useful to evaluate the severity of coartation and the pulsatility of abdominal aorta.

If BP is normal and without consequences: there is no need for regular examination. Thoracic cardiovascular MRI after surgery should be performed at 10–14 years of age.

BAV: The periodicity of evaluation will depend on aortic dimension and function: annually if ascending aorta is dilated. Calcification may occur with age and may cause functional impairment (aortic stenosis or regurgitation) [28]. *A thoracic MRI should be performed at adolescence.*

AoVD: The periodicity of evaluation will depend on the severity of valvular pathology, if severe aortic regurgitation, every 6 months. Pulse and continuous Doppler should be used for the evaluation of the gradient and valvular area in the different projections. The periodicity of evaluation will depend on the severity of valvular pathology, if severe aortic regurgitation, every 6 months.

PPAVD: No need for follow-up 1 year after surgical repair.

Mitral valve prolapse: Check up every 1–2 years only if mitral regurgitation is significant.

References

[1] E. Surerus, I.C. Huggon, L.D. Allan, Ultrasound Obstet. Gynecol. 22 (2003) 264–267.
[2] E.B. Clark, Teratology 29 (1984) 355–361.
[3] L. Mazzanti, E. Cacciari, Italian Study Group for Turner Syndrome (ISGTS), J. Pediatr. 133 (1998) 688–692.
[4] M.L. Loscalzo, et al., Pediatrics 115 (2005) 732–735.
[5] D.F. Gunther, et al., Pediatrics 114 (2004) 640–644.
[6] C.O. Gøtzsche, et al., Arch. Dis. Child. 71 (1994) 433–436.
[7] V.P. Sybert, Pediatrics 101 (1998) 1–7.
[8] D. Prandstraller, et al., Pediatr. Cardiol. 20 (1999) 108–112.
[9] T.M. Volkl, et al., Clin. Cardiol. 28 (2005) 88–92.
[10] W.H. Price, F. Willey, J. Med. Genet. 17 (1980) 133–134.
[11] A.G. Van Wassenaer, L.J. Lubbers, G. Losekoot, Eur. J. Pediatr. 148 (1988) 101–103.
[12] J.W. Moore, et al., Pediatrics 86 (1990) 273–276.
[13] S.M. Bechtold, et al., Eur. J. Pediatr. 163 (2004) 158–162.
[14] A.E. Lin, et al., J. Pediatr. 109 (1986) 820–826.
[15] A.E. Lin, B. Lippe, R.G. Rosenfeld, Pediatrics 102 (1998) 1–9.
[16] P. Saenger, et al., J. Clin. Endocrinol. Metab. 86 (2001) 3061–3069.
[17] M. Elsheikh, et al., Endocr. Rev. 23 (2002) 120–140.
[18] V.B. Ho, et al., Circulation 110 (2004) 1694–1700.
[19] J.E. Ostberg, et al., J. Clin. Endocrinol. Metab. 90 (2005) 5161–5166.
[20] F. Chalard, et al., Pediatr. Radiol. 35 (2005) 323–326.
[21] J.E. Ostberg, et al., J. Clin. Endocrinol. Metab. 89 (2004) 5966–5971.
[22] M.J. Roman, et al., Am. J. Cardiol. 64 (1989) 507–512.
[23] R.M. Lang, et al., J. Am. Soc. Echocardiogr. 18 (2005) 1440–1463.
[24] L. Mazzanti, et al., in: P. Saenger, A.M. Pasquino (Eds.), Optimizing Health Care for Turner Patients in the 21st Century, Elsevier, Amsterdam, 2000, pp. 125–136.
[25] K.L. Dawson-Falk, et al., Australas. Radiol. 36 (1992) 204–209.
[26] A.V. Castro, et al., Arq. Bras. Cardiol. 78 (2002) 51–58.
[27] P.A. Seirafi, et al., Ann. Thorac. Surg. 66 (1998) 1378–1382.
[28] G.S. Conway, Growth Horm. IGF Res. 14 (2004) S77–S84.