CLINICAL STUDY

Cardiovascular findings and management in Turner syndrome: insights from a French cohort

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Abstract

Objective: Congenital cardiovascular malformations and aortic dilatation are frequent in patients with Turner syndrome (TS). The objective of this study was to investigate the cardiovascular findings and management in a large cohort of patients, including children and adults.

Design/methods: We recruited 336 patients with TS from a network of tertiary centers. We reviewed their files, checking for cardiovascular events, cardiac valve abnormalities, and aortic diameters indexed to body surface area (BSA) from magnetic resonance imaging ($n=110$) or echocardiography ($n=300$).

Results: Informative cardiovascular data were available for only 233 patients. Vascular surgery was reported in 7.4% of the cohort. The first cause of surgery was aortic coarctation, detected in 6.9% at a median age of 9.5 (range: 0–60) years. Bicuspid aortic valve (BAV) was detected in 21% at a median age of 20 years (25th–75th percentiles: 15–30). At least one aortic diameter exceeded 32 mm in 12% of the cohort. This was detected at a median age of 19 (7–30) years. When indexed to BSA, at least one aortic diameter exceeded 20 mm/m² in 39% of the cohort.

Conclusion: Our study shows that cardiovascular monitoring for TS patients is currently insufficient in France. BAV is present at birth, but often remains undiagnosed until later in life. Therefore, improved management in cardiovascular monitoring is required and a more systematic approach should be taken.

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Introduction

Turner syndrome (TS), affecting 1/2500 liveborn girls, results from the total or partial absence of the X chromosome. Mortality rates are three times higher in women with TS than in the general female population (standardized mortality ratio=3.0; 95% confidence interval (95% CI) 2.7–3.4) (1). These higher mortality rates are largely due to cardiovascular complications, such as aortic dilatation and dissection.

The estimated incidence of dissection is 36/100 000 TS years vs only 6/100 000 in the general population (2).

In the last few years, several recommendations for the medical follow-up of patients with TS have been published (3). Monitoring is based on expert consensus. Cardiovascular screening includes blood pressure measurement, echocardiography, and cardiovascular magnetic resonance imaging (MRI). It has been recommended that, in the absence of cardiovascular disease, echocardiography or MRI should be carried out

every 5–10 years. Annual imaging is recommended in cases of an aortic diameter >32 mm or 20 mm/m² (3, 4). Unfortunately, several studies have suspected suboptimal diagnosis despite high cardiovascular mortality (1, 5, 6). The aim of this study was to investigate cardiovascular findings and management in a large cohort of French patients with TS, including infants, children, adolescents, and adults. For this purpose, we reviewed the medical charts of patients. We investigated the occurrence and timing of cardiovascular abnormalities to assess the standardization of cardiovascular follow-up in patients with TS.

Materials and methods

The French Ministry of Health set up the Reference Center for Rare Growth Disorders (CMERC) in Paris in 2006. This network of specialized tertiary centers was established to improve and harmonize the care of patients with these rare diseases during the transition from adolescence to adulthood. It brings together the endocrine units of the Saint-Antoine, Robert-Debré, Pitié-Salpêtrière, Armand Trousseau, Necker, and Bicêtre Hospitals. Patients' files are recorded in a web database called CEMARA. This database has been declared to the French data protection agency (CNIL). We studied the cohort of patients followed up at this center between January 1999 and April 2009. This cohort includes patients with TS diagnosed between 1954 and 2008. The study was approved by the Institutional Review Board of our faculty.

The patients with a standard peripheral leukocyte karyotype, with more than 10% of cells displaying a total or partial loss of the X chromosome, were eligible. We considered the following data for each patient: age at diagnosis of TS, timing of cardiac and aortic surgery, timing, and results of the most recent echocardiogram and/or MRI.

Two-dimensional echocardiography of the aortic root was performed at end-diastole in the parasternal long-axis views at four levels: the aortic annulus, the aortic sinuses, the supra-aortic ridge, and the proximal ascending aorta, as described by Roman *et al.* (7). We also collected data concerning valve morphology, according to the European Association of Echocardiography (8).

Patients underwent imaging on a 1.5 Tesla MRI scanner. Aortic diameters were measured at the level of the aortic cusps, the aortic sinuses, the supra-aortic ridge, the proximal ascending aorta, the aortic arch, and the descending aorta. Standardized imaging included morphologic ECG-gated sequences in the axial, coronal, and left-anterior-oblique axes and cine-MR sequences in a coronal view of the ascending aorta and through the aortic valve to check for aortic regurgitation or stenosis and to determine valve morphology (9, 10, 11).

For each patient, we recorded the largest aortic diameter (mm) at the most recent cardiovascular

examination, together with height, weight, and BMI of the patient at the time of that examination. Body surface area (BSA) was calculated according to the formula of Dubois & Dubois (12). According to the previous recommendations (3, 4), aortic dilatation was defined as an aortic diameter exceeding 32 mm or 20 mm/m². In cases of 'normal' cardiac evaluations with no documentation of aortic diameter, the patient's file was excluded from the analysis.

We first focused on the most recent cardiological screening and then searched the file to determine the time at which any abnormalities were first noted. The original cardiovascular reports were looked for in each patient's file. We excluded patients ($n=13$) whose most recent cardiovascular examination had taken place before 1998 (Fig. 1).

Statistical analysis

The characteristics of the patients were expressed as frequencies and percentages for categorical variables and as mean $\pm$ s.d. or median (25th–75th percentiles) and range for continuous variables. Relationships between categorical variables were assessed with χ^2 tests.

We used the Kaplan–Meier method to generate survival curves from birth and to determine survival rates and their 95% CIs (Greenwood variance). The events studied were BAV, aortic coarctation, and aortic dilatation. Analysis was carried out with the SAS V9.2 System (SAS Institute, Cary, NC, USA) and R software version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org) for analyses of agreement and survival.

Results

Our cohort included a total of 336 women with TS seen at our center between 1999 and 2009. No detailed cardiovascular monitoring was carried out in 20 of the

Figure 1 Flow chart of the cohort.

336 cases (5.9%; Fig. 1). Cardiovascular tests were presumably carried out but no cardiovascular data were available for ten cases (3%) and data available before 1998 in 13 cases were excluded. In 60 cases (17.8%), cardiovascular imaging results were reported as 'normal' with no written record of the aortic diameter measured. Informative cardiovascular data were therefore available for 233 patients.

The clinical characteristics of these patients are reported in Table 1. In summary, 73 children (31.3%) and 160 adults were analyzed. A monosomy was present in 108 of the 233 patients (46%). The other karyotypes observed were 46,Xi(Xq) (21%), 45,X mosaicism (16%), 45,X/46,XrX (9%), 45,X/Y + mosaicism (4%), 46,XdelX, and others (4%). The mean age at diagnosis of TS was 8.0 ± 7.9 (range: 0–50) years. Mean age at diagnosis was 4.9 ± 5.1 years for pediatric units and 9.4 ± 8.5 years for adult units ($P=0.003$). Mean age at most recent cardiac evaluation was 21.6 ± 11.8 (range: 0–67) years. Mean delays from the age at general diagnosis of the syndrome to the age at diagnosis of aortic coarctation and BAV were 3.9 (range: 0–30) years and 13 (range: 0–30) years respectively.

Cardiovascular surgery had been carried out on 17 of our 233 patients (7.4%). No dissection was reported. Median age at surgery was 1 year (range: 0–48 years). Most of the surgical procedures were carried out to correct aortic coarctation ($n=12/17$; 70.5%), at a median age of 0.5 years. In the cohort, 59% of these operations occurred before the age of 5 years, ranging from 0 to 16 years. The second most frequent surgical procedure was valve surgery ($n=5/17$; 29.4%): aortic commissurotomies ($n=3$) performed at the ages of 0, 9, and 16 years; aortic valve replacement ($n=1$); and transcatheter pulmonary valvuloplasty at the age of 2 years ($n=1$). Combined surgery was carried out in seven patients. In three cases, atrial or interventricular septal defects were corrected together with surgical aortoplasty at the ages of 1, 19, and 32 years respectively. In three other patients, BAVs were corrected together with aortic coarctation at birth

Table 1 Population studied: values are expressed as mean $\pm$ s.d. All patients under the age of 18 years were considered to be children.

	Total ($n=233$)	Children ($n=73$)	Adults ($n=160$)
Age at diagnosis of TS (years)	8.0 ± 7.9	4.9 ± 5.1	9.4 ± 8.5
Age at last cardiac examination (years)	21.6 ± 11.8	9.4 ± 5.2	27.2 ± 9.6
Height at last cardiac examination (cm)	141.5 ± 23	121.0 ± 31	150.7 ± 7.7
BMI at last cardiac examination (kg/m^2)	22.2 ± 4.8	19.3 ± 4.8	23.6 ± 4.3
BSA at last cardiac examination (m^2)	1.32 ± 0.3	1.0 ± 0.4	1.5 ± 0.2

BSA, body surface area (10).

Figure 2 Disease-free survival from birth without BAV or aortic dilatation. We used the Kaplan–Meier method to generate survival curves from birth and to determine survival rates without detection of an event and their 95% confidence intervals (Greenwood variance). The events studied were detection of BAV and aortic dilatation. (a) Disease-free survival without bicuspid aortic valves (BAV). (b) Disease-free survival without aortic dilatation.

in two patients and at the age of 16 years for the last patient.

The remaining patient underwent coronary artery bypass grafting for coronary atherosclerosis together with aortic surgery at the age of 48 years. Three surgical procedures – pulmonary valve surgery or correction of aortic dilatation – were performed in patients aged 19, 32, and 48 years. One patient underwent surgery for aortic stenosis at the age of 9 years. In one case, surgery for a dilated subclavian artery was performed at the age of 16 years.

Echocardiography and MRI data were available for 222 and 101 cases respectively. In total, 90 patients (38.6% of the cohort) underwent both echocardiography and MRI. Cardiological evaluation revealed no abnormality in 131 cases (56.2%).

BAVs were detected in 49 patients (21%), with an age at diagnosis ranging from 0 to 66 years. BAV was detected before the age of 5 years in only ten cases. For the remaining patients, the median age of detection of BAV was 20 years (25th–75th percentiles: 15–30). Survival without the detection of BAV after 20 years of follow-up was 83.2% (95% CI 77.6–88.9; Fig. 2a).

Aortic coarctation was detected in 16 cases (6.9%), at a mean age of 9.5 ± 16 (range: 0–60) years and abnormalities were detected before the age of 5 years in 60% of cases. Other malformations were minor and included pulmonary ($n=17$) and tricuspid ($n=45$) insufficiencies, trivial mitral insufficiency ($n=32$), aortic insufficiency (grade I–II; $n=29$), persistent left superior vena cava ($n=6$), dysmorphic pulmonary veins ($n=2$), and transverse aortic arch elongation ($n=1$).

At least one aortic diameter exceeded 32 mm in 28 cases (12%) and 35 mm in ten cases (4.3%). The median age at detection of aortic dilatation (indexed to BSA) in our cohort was 19 (25th–75th percentiles: 7–30; range: 0–67). Survival without the detection of aortic dilatation after 20 years of follow-up was 77.8%

Figure 3 Aortic diameters at the level of Valsalva sinus according to age at most recent examination. The dotted line represents the limit of 32 mm (left) and 20 mm/m² (right). (a) Shows crude diameters and (b) shows indexed levels (mm/m²).

(95% CI 72.6–83.5; Fig. 2b). When aortic diameter was indexed to BSA, 91 (39%) patients from the cohort had at least one aortic diameter > 20 mm/m² (Fig. 3).

In total, 27 of the 49 cases of BAV presented an aortic diameter > 20 mm/m². Aortic dilatation was therefore more frequent in patients with BAV than in patients without BAV (62.5 vs 31.3%, $P < 0.001$). A 45,X karyotype was present in 63% of the patients with BAV and only 37% of those without BAV ($P = 0.007$). Furthermore, a 45,X karyotype was present in 57.9% of patients with aortic dilatation and 42% of patients without aortic dilatation ($P < 0.009$).

Discussion

Our observational study included 336 patients with TS. It constitutes a large population, including infants, children, adolescents, and adult patients, followed over a long period. Most studies on cardiovascular status in patients with TS have included less patients (13, 14, 15). The largest study by Mazzanti *et al.* (16) included 594 patients with TS aged 1 month to 24 years. In our study, we included patients up to the age of 60 years. In our population, the mean age at diagnosis of TS was 8.0 ± 7.9 years. The statistically significant difference between ages of diagnosis in pediatric and adult units ($P = 0.003$) suggests that the age at diagnosis is improving over time in our tertiary center. In other cohorts from US or Sweden, the age at diagnosis reached 14.5 (1) or 15.1 years (95% CI 14.5–15.8) (17).

We considered it very important to evaluate current care of patients with TS. So far, few prospective studies on cardiac outcomes have been reported in patients with TS (15). Among 17 patients, MRI detected aortic anomalies in seven patients, and the time to lesion detection was between 2 and 6 years in adults with TS (18). In an Italian cohort of 80 adults, aortic diameter increased with growth rates of 0.1–0.4 mm/year (19).

Informative cardiovascular data were available for only 233 of our cases. Despite the follow-up of these patients at a reference center, cardiovascular evaluation was not carried out in 5.9% of cases. Furthermore, reports of evaluations summarized the findings as 'normal' rather than giving precise aortic diameters in millimeters for 17.8% of the patients. Our study highlights the need for improvement, with cardiovascular monitoring being made systematic in patients with TS. Interestingly, a recent study showed that only 3.5% of patients with TS are being followed in accordance with National Institute of Health recommendations (20). The authors of this previous study highlighted the contribution of the loss of patients during the transition from pediatric to adult care. However, missing cardiovascular data rates in our cohort did not differ between children and adults. Freriks *et al.* (6) have recently reported in 150 patients that standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with TS. As a result of our study, we have set up cardiovascular forms to be completed by physicians. We are planning to evaluate in 2 years, time the efficacy of this procedure on improving cardiovascular follow-up. As our study is only an assessment of referred patients, our findings cannot be extrapolated to the entire population of patients with TS.

Among our informative patients, no cardiovascular abnormalities were observed in 56.2% of the cohort. This percentage is not very different from previous studies (9, 14, 21).

BAVs were detected in 21% of cases. The prevalence of this abnormality was identical in children and adults. Sachdev *et al.* (13) previously reported a prevalence of BAV, as assessed by highly focused echography and MRI, of 30%. Interestingly, although BAVs are present at birth, we found that they were frequently detected much later in life, at a mean age of 19.1 ± 14.8 (range: 0–66) years. Echocardiography was carried out by trained physicians at our reference center, but this examination can be difficult to carry out in infants and children and may fail to detect BAV due to pectus excavatum or limited acoustic windows.

In our cohort, aortic coarctation was detected much sooner than BAV, at a mean age of 9.1 years, with ten cases identified before the age of 5 years. Our present findings could be influenced by the well-known general delay in diagnosis of TS (17). Indeed, delayed cardiovascular screening may be due to late diagnosis of TS. This seems to be true for BAV, as the mean delay

between TS diagnosis and BAV diagnosis in our cohort is 13 years, ranging from 0 to 30. However, it does not seem to be the case for aortic coarctation, as the mean delay is rather short (3.94 years). Data on BAV could indicate that cardiac diagnosis in particular is poor, even in the presence of a timely cardiac assessment for all patients in a reference center. Concerning the differences in diagnosis delay between BAV and aortic coarctation, we cannot exclude that our population might have higher rates of unknown aortic coarctation, as previously demonstrated in other cohorts (14, 15). Hence, this supports the fact that all patients with TS should be subjected to a systematic cardiovascular review (3). The consequences of this screening are important in terms of cardiovascular risk prevention.

In our population, we found that 39% of the patients with BSA indexation had a dilated aorta (Fig. 3). This percentage is high, even though our observational study might have underestimated the amount of dilated aorta. The relationship between aortic dilatation and BAV was significant ($P < 0.001$), as suggested in previous studies (13, 22). All our patients with an aortic diameter > 32 mm are alive and none underwent cardiac surgery between 2009 and 2011.

We confirmed statistically significant relationships between the 45,X karyotype and BAV and between 45,X and aortic dilatation. We therefore conclude that patients with X monosomy should have more frequent cardiovascular follow-up. The natural history of aortic dilatation remains unknown in patients with TS. An intrinsic abnormality of elasticity in the ascending aorta has been suggested (23), involving disruption of the transforming growth factor β pathway (24, 25).

In summary, our study sheds further light on the cardiovascular features in TS. It emphasizes the fact that cardiovascular monitoring for TS patients is currently insufficient in France. Furthermore, BAV is present at birth, but it often remains undiagnosed until later in life. Careful cardiovascular monitoring is thus required, and a more systematic approach should be taken.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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