Prevalence and progression of aortic dilatation in adult patients with Turner syndrome: a cohort study

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Abbreviations: ASI: aortic systolic index; AD: aortic dilatation; BAV: bicuspid aortic valve; BSA: body surface area; IQR: inter-quartile range; MRI: magnetic resonance imaging; SMR: standard mortality ratio.

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ABSTRACT

Objective

Turner syndrome (TS) is a rare disorder affecting 1/2500 female newborn. Aortic dilatation (AD) and aortic dissection represent a major concern in TS. The aims of our study were to describe the aortic root growth, potential aortic dilatation (AD) risk factors and cardiovascular outcomes in a cohort of patients with TS.

Methods

Among 204 adult patients included, 197 were studied using a standardized 1.5 Tesla magnetic resonance imaging (MRI) protocol. AD was defined as an aortic diameter ≥20 mm/m² at the Valsalva sinuses and/or at the ascending aorta, when indexed to body surface area.

Results

At baseline, AD was present in 81/197 (41.1%) and 32/197 (16.2%) of patients, at the levels of Valsalva and ascending aorta, respectively. The aortic Valsalva diameter was larger in patients treated for thyroiditis ($p<0.001$). Potential risk factors of AD were aging ($p< 0.001$) and presence of bicuspid aortic valve (BAV) ($p= 0.002$). The hazard ratio (HR) of AD occurrence in the presence of BAV was 2.2 (95%CI 1.33-3.71). After a median follow-up period of 5.1 years (n=143), AD was present in 58/143 (40.6%) and 25/143 (17.5%) of patients at the levels of Valsalva and ascending aorta, respectively. The median aortic growth of the Valsalva sinuses remained stable. At the ascending aorta, it increased by 0.14 ±0.61 mm/year. Only one aortic-related death was observed.

Conclusion

AD is common in adult patients with TS. However, our results are rather reassuring, as the median aortic diameters remained stable after 5.1 years and few aortic events were observed.

INTRODUCTION

Turner syndrome (TS) is a rare disorder (ORPHA #881) which affects 1/2500 female newborns and is characterized by the complete or partial loss of the second X chromosome. The associated clinical conditions include growth failure (95-100% of cases), primary ovarian insufficiency (95%), autoimmune disease (58%), as well as congenital or acquired cardiovascular disease (1).

Congenital cardiovascular malformations are present in about half of patients with TS (2). The most frequent one is bicuspid aortic valve (BAV), occurring in 20% to 30% of TS (3). In the general population, its prevalence is 2-3% in males and 0.05% in females (4). It has been reported that the prevalence of BAV and other congenital cardiovascular malformations are more frequent in patients with a homogenous 45,X karyotype than in patients with 45,X/46,XX mosaicism (1, 5). BAV is associated with proximal aortic dilatation (AD) and is a predisposing risk factor for subsequent aortic dissection (2). In patients with BAV or Marfan syndrome, beta-blocker or losartan treatments are recommended when AD is detected (2, 6).

The mortality of patients with TS is increased three-fold when compared to the general population (SMR=3.0; 95%CI 2.7-3.4) (7), in association with the occurrence of cardiovascular diseases including aortic dissection. The incidence of aortic dissection diagnosed by echocardiography in a cohort of Swedish women with TS, after 23 years of follow-up, was 110 cases/100 000 patients-years (8). The risk factors of aortic dissection in this study were the presence of AD, hypertension, BAV and aortic coarctation. However, in 11% of the cases reported in the literature, TS by itself was an independent risk factor of

aortic dissection (9). European guidelines concerning screening for AD in TS have been published in 2017 (2). They recommend measuring aortic root diameters at reference levels, such as the aortic annulus, Valsalva sinuses, sinotubular junction as well as ascending aorta and indexing the aortic diameter to the adult patient's body surface area (BSA) (2). The primary objective of our study was to describe the aortic root growth using standardized screening by magnetic resonance imaging (MRI) in a large cohort of adult patients with TS. The secondary objectives were to identify risk factors of AD and to describe the cardiovascular outcomes.

PATIENTS AND METHODS

PATIENTS

Adult patients with TS were recruited in our unit, labeled by the French Ministry of Health as a *Reference Center for Rare diseases of Growth Disorders and development* since 2006. This center belongs to the national endocrine rare disease network named FIRENDO (firendo.fr), and to the Endo-ERN network (endo-ern.eu; id 739527).

To be included, each patient had a standard karyotype on blood cells with at least 10% of cells displaying a total or partial loss of one X chromosome. This observational study was approved by the Paris Nord Ethics Review Committee for Biomedical Research Projects (CEERB) (N° 12-029). All the patients' files were included in the CEMARA database. This national database has been declared to the French data protection agency (Commission Nationale de l'Informatique et des Libertés (CNIL), N° 909474 in 2010). In compliance with

French law, consent of non-opposition to collect and use the data was obtained from each patient.

Data collected for the present study included the patient's date of birth, auxological data, karyotype and previous history of surgery. Congenital heart malformations, such as bicuspid aortic valve (BAV) or other valvulopathies and aortic coarctation were recorded, as well as past and present medical treatments. BSA was calculated according to Dubois' formula (10). Automated office blood pressure readings were obtained in the seated position, with an appropriate cuff size at the level of the patient's right atrium, as recommended (2). Diagnosis of thyroiditis was established by TSH level and/or the presence of anti-thyroid antibodies (anti-thyroperoxydase and anti-thyroglobulin), as recommended (2). When patients were treated with L-thyroxin at the time of inclusion, they were defined as under treatment.

IMAGING

All patients were scanned using the same acquisition protocol for baseline and follow-up imaging with a 1.5 Tesla MRI (Signa HDxt; GE Medical Systems; Wisconsin; USA). A standard non-contrast MRI protocol with a dedicated phased-array cardiac coil and retrospective ECG gating was performed. Gradient echo localizers were used to obtain anatomic axes of the aorta. Cine b-SSFP imaging was performed in coronal oblique view (or left ventricular outflow tract 2 – LVOT 2 view), sagittal oblique view and axial oblique view centered on the aortic valve. Aortic diameters were assessed for all aortic MRI scans by experienced cardiovascular radiologists on a dedicated workstation (Carestream Health; Rochester; NY) using the coronal oblique and sagittal oblique cine images at the Valsalva sinuses and tubular ascending aorta. Measures were obtained using the classic inner edge to inner edge

method in diastole (11). Aortic valve morphology and assessment for aortic regurgitation and/or stenosis were evaluated with cine axial oblique images. The intraclass correlation coefficient (ICC) and its 95% confidence intervals (CI) (estimated by bootstrap) were used to assess the concordance of measurements between 3 operators from the same radiology department for Valsalva and ascending aorta measurements in a sample of patients: the ICC are 0.83 (CI95% 0.35-0.90) and 0.84 (CI95% 0.47-0.92) for MRI measurements at the Valsalva level and at the ascending aorta level, respectively.

Aortic dilatation

AD was defined as an absolute aortic diameter at the Valsalva sinuses and/or at the ascending aorta larger than 32 mm and/or ≥20 mm/m², when indexed to BSA. Aortic systolic index (ASI) was defined as the ascending aorta diameter indexed to BSA (2).

Aortic root growth

When at least two MRIs were available, kinetics of aortic root diameters were systematically assessed at the Valsalva sinuses and ascending aorta. The rate of progression was expressed in millimeter per year (mm/y) and was defined as: (last MRI aortic diameter – first MRI aortic diameter [mm])/ (elapsed time between the last and the first MRI [year]). As previously described, the threshold of 1 mm/year was used to define rapid aortic growth (12).

STATISTICAL ANALYSIS

Baseline characteristics were expressed as frequency and percentage for categorical variables and as median (interquartile range, IQR) for continuous variables. Mean baseline absolute aortic diameter at the Valsalva level was compared between patients according to

the presence of BAV and/or treated thyroiditis using a one-way ANOVA test. Mean baseline aortic diameter was also compared according to treated thyroiditis in patients with and without BAV by using Student's t test (Bonferroni correction, p-value <0.025).

AD-free survival, according to the presence of BAV, was represented using Kaplan-Meier survival curves in the population with at least one informative MRI. Risk factors of AD occurrence were evaluated using a Cox proportional hazard model. Age, interaction variable between age at diagnosis of TS and past GH treatment were forced in the model. Presence of BAV, past aortic surgery, aortic coarctation, an homogenous 45,X karyotype and treated cardiovascular risk factors were selected in univariate analysis (p-value <0.20). Proportional hazard and log-linearity hypothesis have been checked. Results were expressed as hazard ratios for Cox models with 95% confidence intervals (CIs).

Progression of the absolute aortic diameter at the Valsalva sinuses and the ascending aorta was studied in the population with at least 2 informative MRIs using a linear regression model. Final models were built using a backward stepwise procedure with covariates selected in the univariate analysis (p-value<0.20). Normality of the aortic diameter progression, log-linearity hypothesis, homoscedasticity and independence of residues have been checked. All analyses were performed with the SAS version 9·4 statistical software (SAS Institute Inc., Cary, NC, USA).

RESULTS:

BASELINE CHARACTERISTICS

Two hundred and four women were included in the cohort, between 2006 and 2019. Among them, a standardized aortic MRI scan protocol at the 2 aortic positions studied was at least performed once for 197 patients and twice for 143 patients (*Figure 1*). Baseline clinical characteristics, karyotypes, medical histories, past and current treatments among 197 patients are reported in *Table 1.* Other observed valvulopathies were aortic insufficiencies (4.9%) and aortic stenosis (0.5%). Cardiovascular surgery had been performed during childhood in 12/197 (6.1%), including isolated aortic coarctation repairs (n=6 patients). Sixty-five patients had thyroiditis. Among them, 43 were positive for anti-thyroid antibodies.

Median baseline aortic diameter at the Valsalva level was 18.9 mm/m² (IQR: 17.2-20.9) (*Figure 2a*). Median ASI was 15.9 mm/m² (IQR: 14.5-17.8) *(Figure 2b)*. At baseline, 83/197 (42.1%) patients had AD: it was observed in 81/197 (41.1%) and 32/197 (16.2%) patients at the Valsalva and at the ascending aorta level, respectively. AD was observed at the ascending aorta but not at the Valsalva level in 2 cases. The median age at patients with baseline AD was 29.4 years (IQR: 20.0-37.4) and 34.8 years (IQR: 25.9-43.0) at the Valsalva and the ascending aorta levels, respectively. Baseline aortic diameter at the Valsalva level was significantly different according to the presence of biscupidy and/or treatment for thyroiditis ($p<0.001$) (*Figure 3*). Among patients with BAV, aortic diameters at the level of Valsalva were larger in patients treated for thyroiditis (31.8±4.5 vs 30.8±3.7; $p<0.001$). Among patients without BAV, a treated thyroiditis also led to larger aortic diameters (28.5±3.7 vs 27.0±3.1; $p<0.001$).

FOLLOW-UP

Aortic dilatation (AD)-free survival

AD was observed in 102/197 (51.8%) patients. The median survival time without AD was 35.0 years. AD occurrence was present in 100/197 (50.8%) and 42/197 (21.3%) patients at the Valsalva and the ascending aorta level, respectively. Using multivariate Cox analysis, both aging ($p< 0.001$) and the presence of BAV ($p= 0.002$) were significantly associated with AD occurrence. It was not associated with past GH treatment, the presence of aortic coarctation, nor a 45,X karyotype. Adjusted hazard ratio (HR) of AD occurrence in patients with BAV was 2.2 (95% CI 1.33-3.71), as compared to those without BAV (*Figure 4*).

Aortic growth

Among the cohort, 143 patients had at least 2 MRIs (*Supplemental Table 1*). These patients were not different from the patients with one MRI (data not shown). Their median number of MRIs was 3.0 (IQR: 2.0-4.0) and their median follow-up was 5.1 years (IQR: 2.8-7.5). At the end of the follow-up period, AD was found in 58/143 (40.6%) and 25/143 (17.5%) at the level of the Valsalva sinuses and ascending aorta, respectively.

At the end of follow-up, mean progression of aortic diameter at the Valsalva sinuses was 0.0 ± 0.80 mm/year. Results from a multivariate linear regression analysis showed an association between baseline aortic diameter, BSA and treated hypertension and aortic growth at the Valsalva ($p<0.05$). At the end of the follow-up, mean progression of aortic diameter at the ascending aorta was 0.14 ±0.61 mm/year. According to a multivariate linear regression analysis, age, baseline aortic diameter and the presence of a valvulopathy different from uncomplicated BAV, were significantly associated ($p<0.05$) with aortic growth.

At the end of the study, 4 patients had a progression of their aortic diameter higher than 1 mm/year at the Valsalva sinuses and 7 others at the level of ascending aorta. Ten of them had an aortic diameter above 25 mm/m² at a median age of 52 years (IQR: 36.5-65.7).

Of these 143 patients, 15 (10.5%) were treated with beta-blockers. Among them, this treatment was prescribed in the presence of AD for 8 patients. Their median age was 36.5 years (IQR: 29.7-40.0). The aortic diameter growth was not significantly different between patients with beta-blockers and those without beta-blocker intake, neither at the Valsalva sinuses (p=0.18), nor at the ascending aorta (p=0.33) levels.

During the follow-up period, 11 patients became pregnant, leading to 13 births. Aortic diameters before and after pregnancy were available for 5 patients (median age: 31.0 years old [IQR: 30-35]). Their aortic growth (mm/year) was not significantly different from the rest of the cohort, both at the Valsalva (p=0.39) and the ascending aorta (p=0.22) levels. The rate of rapid progression (> 1 mm/year) was not different between pregnant and non-pregnant patients (p=0.20).

Cardiovascular outcomes

During the follow-up period, 2 patients had prophylactic aortic surgery for AD. ASI values at the time of surgery were 38 mm/m² and 25 mm/m² for each of these patients.

Three patients had died at the end of the follow-up period. One death was related to an aortic dissection in a 65-years-old patient with a major AD (44 mm at the Valsalva sinuses; 30.13 mm/m²). She had previously declined aortic surgery. The second death occurred in a 39-years-old patient who had cardiorespiratory arrest after surgery for a grade IV mitral

insufficiency. The third death occurred after a second episode of stroke in a 70-years-old hypertensive patient. Finally, a 33 year-old patient presented a spontaneous dissection of her right vertebral artery. Her aortic diameter, measured 6 months before this vascular event, was 32 mm (19.9 mm/m²) at the Valsalva sinuses. She progressively recovered from this episode and completed the study.

DISCUSSION

Our study evaluated the cardiovascular outcomes of a large cohort of adult patients with TS who had at least one 1.5 Tesla MRI, measuring aortic diameters both at the Valsalva and the ascending aorta levels. At baseline, AD was observed in 81/197 (41.1%) and 32/197 (16.2%) patients, at the Valsalva and ascending aorta levels, respectively. At the end of the follow-up period, AD was present in 58/143 (40.6%) and 25/143 (17.5%) at those same levels, respectively.

We show that the presence of BAV was significantly associated with the occurrence of AD. Furthermore, we were able to quantify the risk of AD according to the presence of BAV, with a hazard ratio (HR) of 2.2 (95%CI 1.33-3.71). AD was found to be much more frequent at the Valsalva level than at the ascending aorta. In a cohort of 253 patients with TS, Sachdev *et al.* showed that "typical" BAV, resulting in anterior and posterior cusps, was frequent and was correlated with AD at the Valsalva level (3). Therefore, a potential explanation of the highest rate of AD at the Valsalva level might rely on this type of BAV. Unfortunately, in our study, data concerning the type of BAV were not available for all patients.

In our study, presence of a treated thyroiditis was associated with baseline AD. Regardless of the presence of BAV, the association remained significant ($p<0.001$). Previous studies addressing congenital aortopathies have shown that systemic auto-immunity and inflammation are present in aortic remodeling. Indeed, proliferation of smooth muscle cells of the aortic media is regulated by cytokines secreted by immune and endothelial cells, whereas muscle remodeling involves the action of metalloproteases and TGF-β-mediated signaling (13). To our knowledge, the present study is the first one reporting a relationship between thyroiditis and AD in patients with TS.

Few studies have evaluated the progression of aortic diameters in adult patients with TS. Mortensen *et al*. (14) studied 91 patients for an average follow-up period of 8.8 years. The aortic progression was 0.32±0.3 mm/year and 0.20±0.2 mm/year at the Valsalva sinuses and the ascending aorta level, respectively. Duijnhouwer *et al.* (15) studied 171 adult patients with TS, screened either by MRI or CT-scan for AD at the tubular ascending aorta level. This study reported a median aortic progression of 0.20 mm/year (IQR: 0.0-0.4)(15). Our results based on the evaluation of aortic diameters of both the Valsalva sinuses and the ascending aorta show a median increases in size of 0.0 ±0.80 mm/year and 0.14 ±0.61 mm/year, respectively. Although AD is more frequent at baseline at the Valsalva level, the increase in aortic diameter size at this level is slower than that at the ascending aorta level. In our study, the progression of aortic diameters is lower than that reported previously. A potential explanation relies on the fact that our population has few cardiovascular risk factors and that median BMI was in the normal range (22.8 Kg/m^2). A past history of ischemic heart disease is present in only 1.5% of the cohort and our population is young, since the median age is 25.6 years.

289 The multivariate linear regression analysis showed that the Valsalva diameter increases with
290 hypertension ($p<0.05$), strongly suggesting that this clinical condition enhances the
291 development of AD. Duijnhouwer *et al.*, using a similar statistical approach, showed that GH
292 treatment was a risk factor for aortic diameter growth (15). However, this result is not
293 confirmed in our study since past GH treatment was related neither to baseline AD, nor to
294 progression of aortic diameters. After multivariate analysis, we found that aortic growth at
295 the ascending aorta was associated with other valvulopathies different from uncomplicated
296 BAV, mainly aortic insufficiency and/or stenosis. Therefore, aortic valve diseases might be
297 involved in aortic diameter growth.
298 At the end of the follow-up period, 10/143 (7.0%) patients experienced a progression of
299 their aortic diameter > 1 mm/year. This prevalence is higher than that (4.6%) reported in the
300 Dutch study (15). This may be due to the fact that we measured two aortic positions, giving
301 2.8% and 4.9% of AD at the Valsalva and the ascending aorta, respectively. However, in our
302 cohort, the number of patients with a rapid increase of their aortic diameter was too low for
303 identifying risk factors for a rapid progression.
304 To our knowledge, the impact of beta-blocker treatments in patients with TS has not been
305 previously reported. In patients with Marfan syndrome, beta-blockers slow the rate of AD
306 (16). Among the patients treated with beta-blockers in the present study, aortic diameter
307 growth did not significantly differ from that in patients without a beta-blocker therapy.
308 However, our study is not powerful enough for demonstrating the protective role of beta
309 blockers in the development of AD.
310 Finally, during our follow-up period, the number of cardiovascular events was low (1.96%)
311 and only one death was related to an aortic dissection. In the Dutch cohort study with a 6.8
312 year follow-up (15), two deaths related to aortic dissection were recorded, both at the age

of 44 years. An American study, including 317 women with a very long follow-up (mean 11 years), reported that cardio-vascular diseases were the main cause of death in TS (17). Therefore, our median follow-up period of 5.1 years in a rather young population probably underestimated the rate of cardiovascular events.

Our study has some weaknesses. It could be argued that among our initial cohort, only 143 patients had performed several MRIs. However, their clinical characteristics were not different from these in the other patients included in the study. Furthermore, patients had up to 8 scans with a maximum follow-up of 11.6 years. During follow-up, some patients had a decrease of the absolute aortic diameter. This could be due to the measurement accuracy of MRI. Concerning pregnant women, although their aortic diameter growth was not significantly different from that in the rest of the cohort, their number was too low for reassuring pregnant patients concerning AD.

In the near future, 4D MRI imaging and measurement of stiffness/distensibility of the proximal aorta should be available (18). Further genetic studies are needed to decipher the molecular mechanisms involved in BAV and AD (19) and, therefore, to improve cardiovascular care in patients with TS.

CONCLUSION

Aortic MRI in a population of adult patients with TS demonstrated a high rate of AD, especially at the Valsalva sinuses. The rate of progression of aortic diameters during the follow up period of five years was low. Few deaths related to cardiovascular events were observed. Although our data are reassuring, a long term screening is required to identify the few patients with a pejorative aortic outcome.

DECLARATION OF INTEREST:

All 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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TABLES and FIGURES:

FIGURE 1:

Flow chart of patients included in the study.

TABLE 1: Baseline clinical characteristics of the cohort (n= 197 patients with TS) in the aortic dilatation (AD)-free survival analysis. Results are expressed as number of patients and percentages, or median value and inter-quartile range (IQR). Missing values (a) n=1; (b) n=2; (c) n=3.

FIGURE 2: Scatterplot showing the baseline values of the aortic diameter (mm) related to the patient's age (X axis). Each dot represents a patient: a) at the Valsalva sinuses (n=197); b) at the tubular ascending aorta (n= 197). The central line represents the regression line and the dotted lines represent the 95% confidence interval.

FIGURE 3: Baseline boxplot of aortic diameter at the Valsalva sinuses, according to the presence (+) or absence (-) of a bicuspid aortic valve (BAV) or a history of treated thyroiditis (T) (n=197). The length of the box represents the interquartile range (distance between 25th and 75th percentiles); the symbol inside the box represents the mean; the horizontal line inside the box represents the median; and the vertical lines issuing from the box extend to the minimum and maximum values.

373 **FIGURE 4:** Kaplan-Meier survival estimator without aortic dilatation (AD) of the Valsalva
374 sinuses according to age (X axis), in the presence (black line) or the absence (dotted line) of
375 aortic bicuspid valve (BAV) (n=197).

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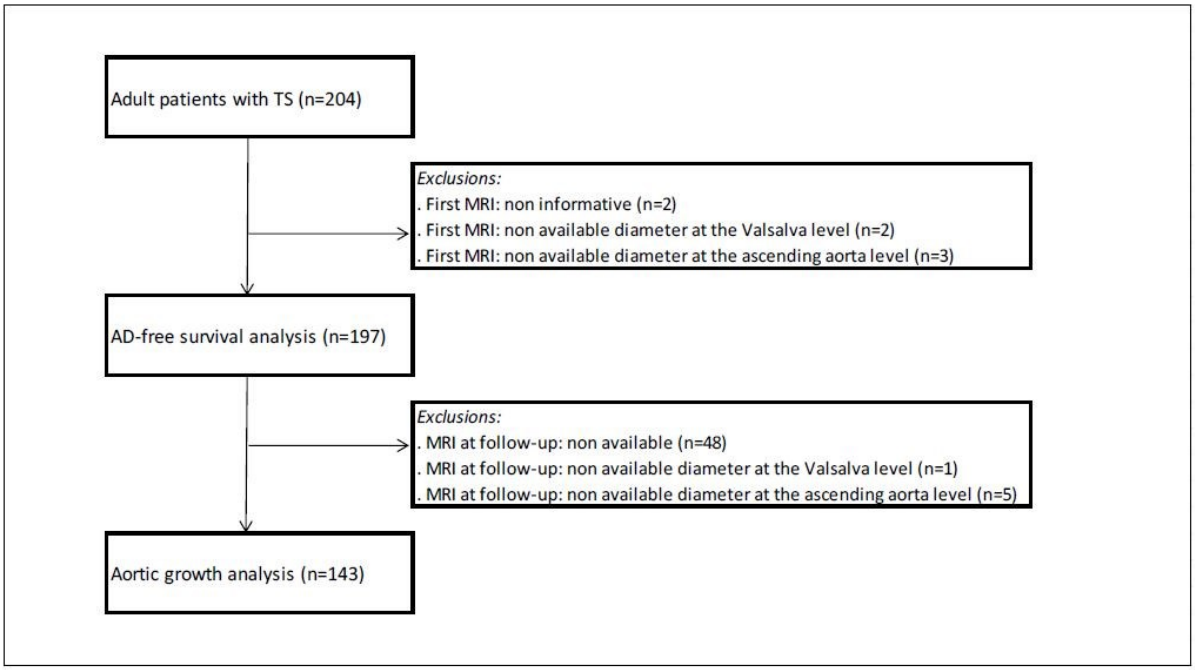
Adult patients with TS (n=204)
Exclusions:
. First MRI: non informative (n=2)
. First MRI: non available diameter at the Valsalva level (n=2)
. First MRI: non available diameter at the ascending aorta level (n=3)
AD-free survival analysis (n=197)
Exclusions:
. MRI at follow-up: non available (n=48)
. MRI at follow-up: non available diameter at the Valsalva level (n=1)
. MRI at follow-up: non available diameter at the ascending aorta level (n=5)
Aortic growth analysis (n=143)

FIGURE 1

	AD-free survival analysis Population (n=197)
	n (%) or median [IQR]
Age (yrs)	25.6 [19.6 ; 34.2]
Years since diagnosis	18.0 [10.0 ; 24.0]
Karyotype	
45,X	79 (40.1)
45,X/i(Xq)+	32 (16.2)
45,X/46,XX	21 (10.7)
45,X/46,Xr(X)	20 (10.2)
45,X/Y+	10 (5.1)
45,X/47,XXX	7 (3.6)
Others	28 (14.2)
Anthropometric values	
Height (cm)	152.0 [147.0 ; 157.0]
Weight (Kg)	52.0 [46.0 ; 60.0]
BMI (Kg/m^2)	22.8 [20.3 ; 25.7]
BSA (m^2)	1.5 [1.4 ; 1.6]
Median blood pressure level (mmHg)	110/70 [102/63;120/77]
Medical history	
Tabagism	23 (11.9) [c]
Diabetes (antidiabetic drug)	12 (6.1) [a]
Dyslipidemia (lipid-lowering drug)	10 (5.1) [a]
Coronaropathy (medical treatment)	3 (1.5)
Hypertension (antihypertensive drug)	9 (4.6)
Past treatment with GH	147 (75.0) [a]
Thyroïdal supplementation	65 (33.2) [a]
Sexual hormonal replacement therapy	177 (90.8) [b]
Aortic coarctation	16 (8.1)
Bicuspid aortic valve (BAV)	45 (22.8)
Valvulopathies different from BAV	24 (12.2)
Basal aortic diameters	
Valsalva level	
(mm/m^2)	18.9 [17.2 ; 20.9]
Dilatation	81 (41.1)
Ascending aorta level	
(mm/m^2)	15.9 [14.5 ; 17.7]
Dilatation	32 (16.2)

TABLE 1

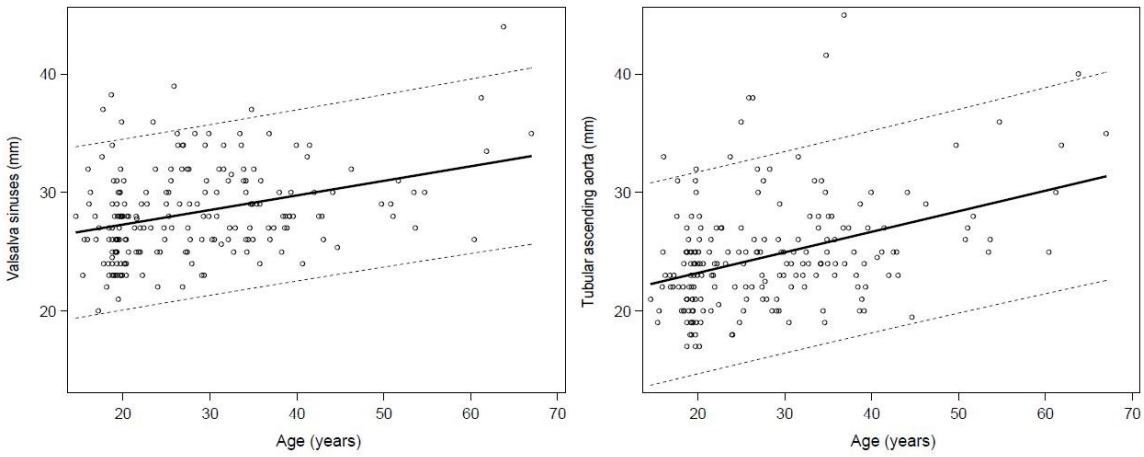
Valsalva sinuses (mm)
Age (years)
Tubular ascending aorta (mm)
Age (years)

FIGURE 2

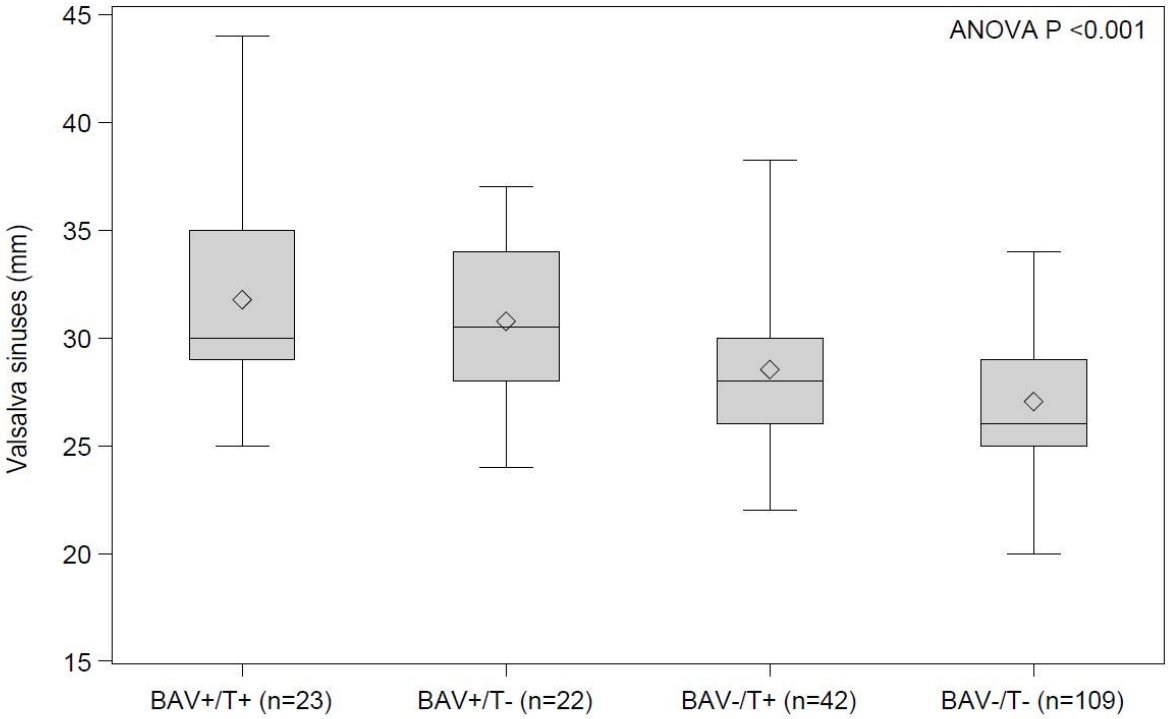
ANOVA P <0.001
Valsalva sinuses (mm)
45
40
35
30
25
20
15
BAV+/T+ (n=23)
BAV+/T- (n=22)
BAV-/T+ (n=42)
BAV-/T- (n=109)

FIGURE 3

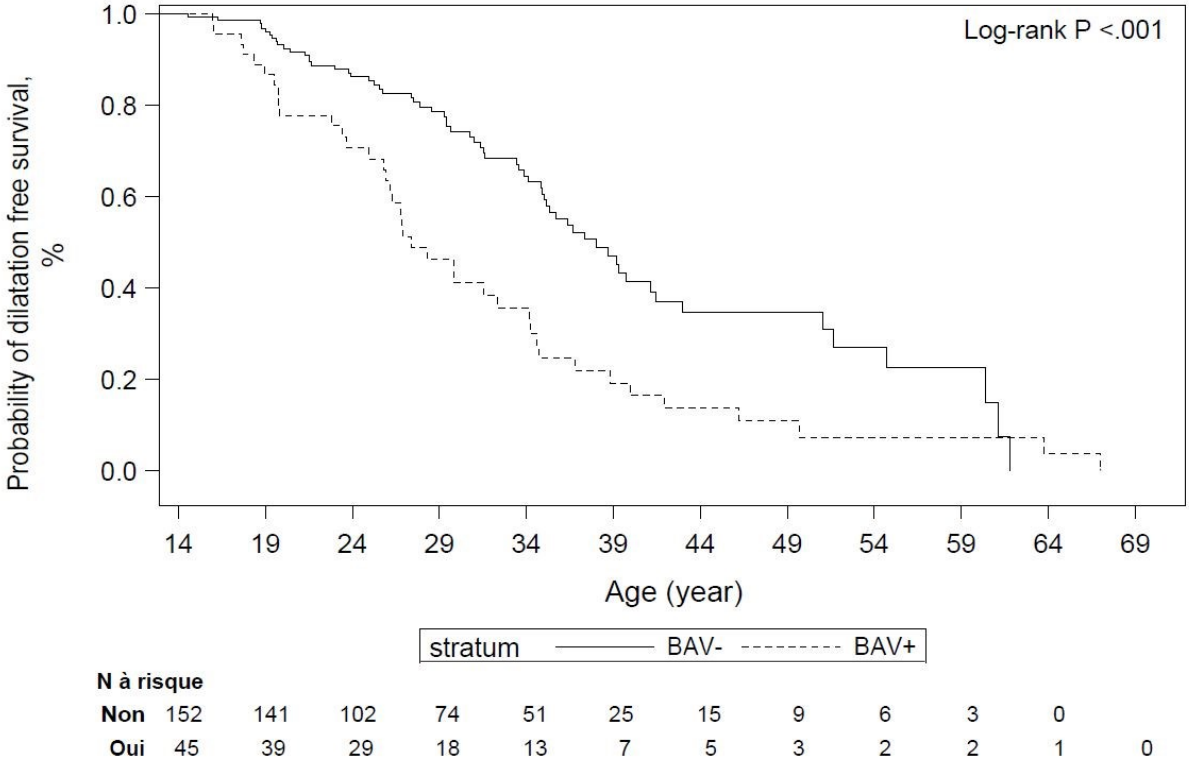
Log-rank P <.001
Probability of dilatation free survival, %
1.0
0.8
0.6
0.4
0.2
0.0
14 19 24 29 34 39 44 49 54 59 64 69
Age (year)
stratum BAV- BAV+
N à risque
Non 152 141 102 74 51 25 15 9 6 3 0
Oui 45 39 29 18 13 7 5 3 2 2 1 0

FIGURE 4

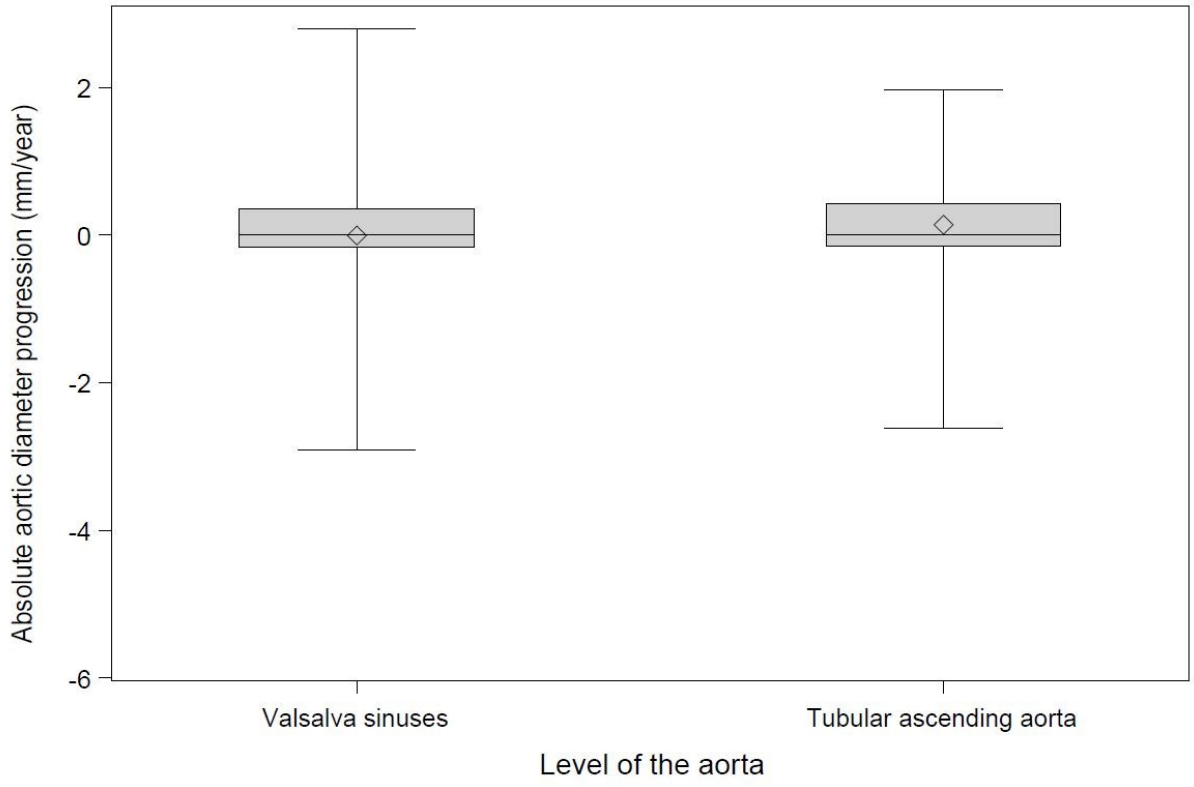
Absolute aortic diameter progression (mm/year)
2
0
-2
-4
-6
Valsalva sinuses
Tubular ascending aorta
Level of the aorta

FIGURE 5

Supplemental TABLE 1: Baseline clinical characteristics of the patient in the aortic growth analysis (n=143 with TS and MRIs at least performed twice). Results are expressed as number of patients and percentages, or median value and inter-quartile range (IQR). Missing values: (a) n=1 ; (b) n=2 ; (c) n=3.

	Aortic growth analysis population
	n (%) or median [IQR]
Age (yrs)	25.6 [19.5; 34.2]
Years since diagnosis	18.0 [11.0; 25.0]
Karyotype	
45,X	61 (42.7)
45,X/i(Xq)+	24 (16.8)
45,X/46,XX	15 (10.5)
45,X/46,Xr(X)	11 (7.7)
45,X/Y+	5 (3.5)
45,X/47,XXX	6 (4.2)
Others	21 (14.7)
Anthropometric values	
Height (cm)	153.0 [146.0; 157.0]
Weight (Kg)	51.0 [46.0; 58.0]
BMI (Kg/m²)	22.6 [20.2; 25.2]
BSA (m²)	1.5 [1.4; 1.6]
Median blood pressure level (mmHg)	116/74 [106/66;126/80]
Medical history	
Tabagism	13 (9.3) [(c)]
Diabetes (antidiabetic drug)	5 (3.5) [(a)]
Dyslipidemia (lipid-lowering drug)	6 (4.2) [(a)]
Coronaropathy (medical treatment)	2 (1.4)
Hypertension (antihypertensive drug)	6 (4.2)
Past treatment with GH	109 (76.8) [(b)]
Thyroïdal supplementation	51 (35.9) [(b)]
Hormonal replacement therapy	129 (90.8) [(b)]
Aortic coarctation	13 (9.1)
Bicuspid aortic valve (BAV)	37 (25.9)
Valvulopathies different from BAV	17 (11.9)
Basal aortic diameters	
Valsalva level	
(mm/m²)	19.0 [17.4; 21.1]
Dilatation	59 (41.3)
Ascending aorta level	
(mm/m²)	16.3 [14.5; 18.3]
Dilatation	24 (16.8)

Supplemental TABLE 1