openheart

Growth of the aortic root in children and young adults with Marfan syndrome

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2022-002097).

To cite: van Elsäcker E, Vink AS, Menke LA, *et al*. Growth of the aortic root in children and young adults with Marfan syndrome. *Open Heart* 2022;**9**:e002097. doi:10.1136/openhrt-2022-002097

Received 21 July 2022
Accepted 21 November 2022

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ABSTRACT

Objectives The primary aim was to gain insight into the growth of the aortic root in children and young adults with Marfan syndrome (MFS). Furthermore, we aimed to identify a clinical profile of patients with MFS who require an aortic root replacement at a young age with specific interest in age, sex, height and fibrillin-1 (*FBN1*) genotype.

Methods Aortic root dimensions of 97 patients with MFS between 0 year and 20 years and 30 controls were serially assessed with echocardiography. Trends were analysed using a linear mixed-effect model. Additionally, including only patients with MFS, we allowed trends to differ by sex, aortic root replacement and type of *FBN1* mutation.

Results Average aortic root dilatation in patients with MFS became more pronounced after the age of 8 years. In the MFS cohort, male patients had a significantly greater aortic root diameter than female patients, which was in close relationship with patient height. There was no difference in aortic root growth between children with dominant negative (DN) or haploinsufficient *FBN1* mutations. However, DN-*FBN1* variants resulting in loss of cysteine content were associated with a more severe phenotype. Eleven children needed an aortic root replacement. Compared with patients with MFS without aortic root surgery, these children had a significantly larger aortic root diameter from an early age.

Conclusions This study provides clinically useful longitudinal growth charts on aortic root growth in children and young adults with MFS. Children requiring prophylactic aortic root replacement during childhood can be identified at a young age. Our growth charts can help clinicians in decision making with regard to follow-up and prophylactic therapy. Loss of cysteine content in the *FBN1* protein was associated with larger aortic root dimensions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Marfan syndrome (MFS) can result in severe aortic root dilatation from an early age. However, comprehensive knowledge on aortic root growth patterns in children with MFS is lacking.

WHAT THIS STUDY ADDS

⇒ The present study is the first study that provides longitudinal growth charts on aortic root growth in children and adolescents with MFS. Using absolute aortic root diameter growth, we found that growth charts can be used to assess aortic root growth at a glance, identifying young patients who may require prophylactic aortic root surgery at an early age. In addition, our study provides important insights into the effect of sex, height and genotype on aortic root growth patterns.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our growth charts can help clinicians in decision making with regard to counselling patients, follow-up frequency and prophylactic therapy.

INTRODUCTION

Marfan syndrome (MFS) is characterised by a weakened, abnormal vascular extracellular matrix caused by mutations in the fibrillin-1 (*FBN1*) gene. This vascular wall abnormality leads to dilatation of the aorta in 60%–80% of patients with MFS, specifically of the aortic root.[1 2] Aortic involvement is generally progressive, and with a growing aortic root diameter, the risk of dissection increases. Currently, clinical management of MFS includes follow-up of the aortic root diameter by serial cardiac imaging, medical treatment with blood pressure-lowering agents (mostly beta blockers and losartan) and prophylactic aortic root replacement.[3] Prophylactic aortic root replacement is generally performed when the aortic root diameter reaches >50 mm, warranting close clinical follow-up of aortic root diameters of every patient with MFS from the time of diagnosis.[4]

Severe aortic root dilatation may start at a very young age. However comprehensive knowledge on aortic root growth patterns in children with MFS is scarce. This is mainly due to the lack of longitudinal data and a great heterogeneity concerning aortic root dilatation among children with MFS. In addition, little is known about the influence of clinical parameters such as age, sex, height and *FBN1*

genotype on the aortic root growth during childhood.[5–7] More insight into aortic root growth patterns in young individuals with MFS may guide clinical decisions on follow-up frequency, medical treatment and need for/timing of prophylactic aortic root replacement.

Accordingly, the aim of this study was to gain insight into the growth of the aortic root diameter in children and adolescents with MFS. Furthermore, we aimed to identify a clinical profile of patients with MFS who require an aortic root replacement at a young age with specific interest in age, sex, height and *FBN1* genotype.

METHODS

All children and adolescents between the ages of 0 and 20 years attending our expert centres for children with MFS in Amsterdam and Leiden between 2016 and 2018 were reviewed for inclusion. MFS was defined according to the revised Ghent criteria.[3] Children with MFS who underwent cardiac surgery other than an aortic root replacement, children with neonatal MFS and children with additional cardiac anomalies were excluded. In addition, a group of healthy control subjects with normal hearts or haemodynamically insignificant cardiac abnormalities was selected from our outpatient clinic database. Control subjects were included if there were two or more echocardiograms available.

Data collection

Of each patient with MFS and control subject, age (in years), weight (in kilogram), length (in centimetre) and blood pressure (in millimetres of mercury) at each consecutive visit were collected from their medical charts. Body surface area (BSA) was calculated using the Haycock-formula.[8] Echocardiographic data were collected from an offline workstation (EchoPac V.11.1.8; GE Vingmed Ultrasound AS, Norway). The diameter of the aortic root, as assessed with echocardiography, was obtained from a two-dimensional parasternal long-axis view during mid-systole. The maximum diameter of the sinus of Valsalva was measured in millimetre (inner edge to inner edge).[9] To correct for height and weight differences, Z-scores were calculated by using the normogram published by Pettersen *et al*.[10]

Pathogenic *FBN1* variants were classified according to the European Molecular Genetics Quality Network (EMQN) guidelines and as described in the recent publication by GP, coauthor of this article.[11] Patients with MFS were stratified into two groups based on the effect of the *FBN1* mutation on the production of the *FBN1* protein: (1) haploinsufficient (HI) *FBN1* mutation carriers, in which the production of normally functioning FBN1 protein is decreased, and (2) dominant negative (DN) *FBN1* mutation carriers, in which a mutant FBN1 protein interferes with the normally functioning FBN1 protein.[12 13] *FBN1* mutations were classified as HI and DN according to the criteria described by Franken *et al*.[14] In addition, *FBN1* variants with a DN effect were further classified by their effect on the cysteine content in the *FBN1* protein, since recent work has suggested an important phenotype correlation.[15 16] The effect of pathogenic *FBN1* variants was predicted using Alamut Visual software (Interactive Biosoftware, Rouen, France).

Follow-up was defined as the period in years from the first echocardiogram until the last available echocardiogram or until the last echocardiogram before an aortic root replacement. According to international consensus, indications for prophylactic aortic root replacement are aortic root diameter of >45 mm on CT scan or >50 mm on echocardiogram or MRI, aortic root growth of >8–10 mm/year or progressive aortic valve insufficiency. In patients with a family history of aortic dissection, the threshold for surgery is an aortic root diameter of >45 mm on echocardiogram.[4 17–19] In our study cohort, surgical interventions were scheduled when aortic root dimensions/growths were near these thresholds.

Patient and public involvement

Patients and/or the public were not involved in the design nor conduct of this study.

Statistical analysis

Analyses were conducted using IBM SPSS Statistics (IBM SPSS Statistics for Windows V.20.0) and R V.3.4.3 (The Foundation for Statistical Computing, Vienna, Austria). Clinical characteristics are presented as number (percentages, %) for categorical data and mean (±SD) for continuous variables with an approximately normal distribution or median (IQR) for continuous data with a skewed distribution. An independent sample t-test or Mann-Whitney U test was used to compare groups.

To estimate the average trends in aortic root growth, we performed a linear mixed-effect model analysis. The aortic root diameter was allowed to vary smoothly by age (fixed-effect) via restricted cubic splines. Knots were placed at five fixed quantiles of age as suggested by Stone and Koo.[20] The intercept (ie, value at birth) and slope were allowed to differ per patient and assumed these parameters to follow a multivariate normal distribution (random effects). Trends were allowed to differ by controls and patients with MFS. Additionally, only including patients with MFS, we performed linear mixed-effect model analyses where the trends were allowed to differ by sex, aortic root replacement or *FBN1* genotype. Sampling uncertainty was shown as 95% CIs. A p value of <0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

The medical records of 151 patients with MFS were reviewed. Forty-three patients (28%) did not meet the revised Ghent criteria; 9 patients had a bicuspid aortic valve (6%); 1 patient (1%) was diagnosed with neonatal MFS; and 1 patient (1%) had undergone aortic and mitral valve surgery, leaving 97 patients with MFS for analysis. Baseline characteristics are shown in table 1. The median follow-up duration was 5.8 years (IQR 3.0–9.2),

Table 1 Characteristics of the study participants during the first and last echocardiographic assessments or last echocardiogram before surgical replacement of the aortic root

Patient characteristics		Marfan syndrome (n=97)	Control group (n=30)	P value
Male (%)		61 (63%)	17 (57%)	0.54
Number of echocardiographs (IQR)		7 (4–11)	3 (2–5)[5]	<0.001
Follow-up in years (IQR)		5.8 (3.0–9.2)	6.4 (4.9–8.1)	0.72
Age in years (IQR)	First echo	5.7 (2.7–8.2)	3.8 (0.2–10.3)	0.22
	Last echo	12.9 (8.2–16.8)	12.2 (6.9–16.3)	0.61
Height for age in Z-score (±SD)	First echo	2.05 (±1.44)	0.50 (±1.09)	<0.001
	Last echo	2.45 (±1.12)	0.80 (±0.90)	<0.001
Weight for age in Z-score (±SD)	First echo	0.62 (±1.02)	0.00 (±1.01)	0.004
	Last echo	0.63 (±0.92)	0.08 (±0.94)	0.005
Systolic BP for age in Z-score (±SD)	First echo	−0.52 (±0.94)	–	–
	Last echo	−0.49 (±0.95)	–	–
Diastolic BP for age in Z-score (±SD)	First echo	−0.09 (±0.79)	–	–
	Last echo	−0.03 (±0.70)	–	–
Aortic root diameter (mm) (±SD)	First echo	25.7 (±6.7)	17.3 (±6.1)	<0.001
	Last echo	33.1 (±7.4)	23.4 (±4.1)	<0.001
Aortic root in Z-score (±SD)	First echo	2.27 (±1.31)	−0.03 (±0.88)	<0.001
	Last echo	2.43 (±1.80)	0.14 (±0.74)	<0.001

BP, blood pressure.

with a median of seven (IQR 4–11) echocardiographic assessments per individual. Of the patients with MFS, 94 (97%) had a pathogenic *FBN1* variant, of which 55 (59%) were DN and 37 (39%) were HI. In two patients, the predicted effect of the *FBN1* mutation was unknown. When focussing on patients with MFS with DN-*FBN1* variants, 24 (44%) children had a *FBN1* variant affecting the cysteine content (15 loss of cysteine content (27%) and 9 gain of cysteine content (16%)).

Control characteristics

A total of 30 control subjects were included (table 1). Of these 30 subjects, 22 (73%) had a small muscular ventricular septal defect (VSD); 5 (17%) had a small atrial septal defect (ASD); 1 subject had both VSD and ASD (3%); 1 subject had a mild pulmonary valve stenosis (maximum 30 mm Hg) (3%); and in 1 subject, no structural abnormalities were observed (3%). The control subjects underwent a median of three echocardiographic examinations (IQR 2–5) during a median follow-up duration of 6.4 years (IQR 4.9–8.1). There was no significant difference in age at first echocardiographic assessment and follow-up duration between the patients with MFS and the control subjects. As expected, children with MFS and control subjects differed significantly in height (Z-score: 2.05±1.44 vs 0.50±1.09, p<0.001), weight (Z-score: 0.62±1.02 vs 0.00±1.01, p=0.004) and number of echocardiographs (p<0.001).

Aortic root growth in patients with MFS

In patients with MFS, the mean aortic root diameter increased from 25.7±6.7 mm at the first echocardiographic assessment to 33.1±7.4 mm during the last echocardiogram, which corresponds to a mean aortic root Z-score of +2.27±1.31 and +2.43±1.80, respectively. In the control subjects, the average aortic root Z-scores at the first and last echocardiogram were significantly smaller (Z-score: −0.03±0.88, p<0.001, and +0.14±0.74, p<0.001, respectively). Individual and average aortic root growths in both groups are shown in figure 1. Patients with MFS had a larger aortic root diameter at all ages compared with the control subjects, even after correction using Z-scores (online supplemental figure S1). There was a significant age-related growth of the aortic root (in millimetre) in both patients with MFS (p<0.0001) and control subjects (p<0.0001). However, the trend differed significantly between the two groups (p<0.0001) with a faster growing aortic root diameter in patients with MFS, which even accelerates at the approximate age of 8 years.

Influence of sex, height and FBN1 phenotype on aortic root diameter growth in patients with MFS

Figure 2 shows the individual and average aortic root growth for male and female patients with MFS. There was a significant difference between the sexes regarding the aortic root growth (p<0.0001). Male patients had a larger aortic root diameter compared with female patients and this difference between male and female patients increases during puberty. When adjusting for height, aortic root growth was not significantly different between male and female patients (figure 3). Finally, online supplemental figure S2 shows aortic root Z-scores for male and female patients throughout childhood. Z-scores

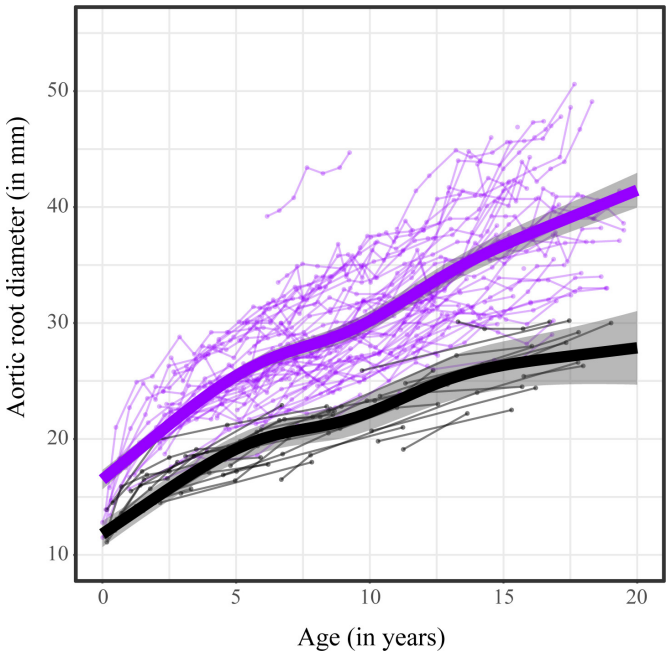

Figure 1 Individual and average aortic root diameters (in mm) in 97 patients with Marfan syndrome (purple) and 30 control subjects (black); 95% CIs are depicted (grey area).

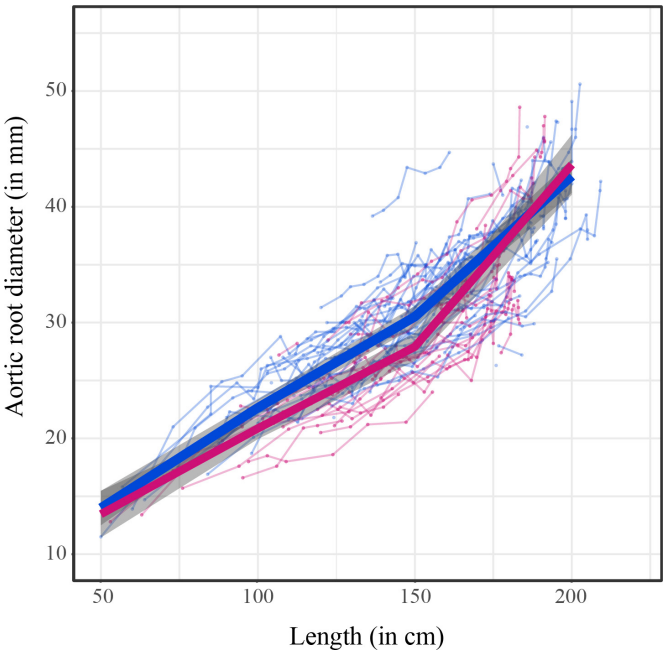

Figure 3 Height (in cm) versus aortic root diameter (in mm) in 61 male patients with Marfan syndrome (blue) and 36 female patients with Marfan syndrome (pink); 95% CIs are depicted (grey area).

in male patients exceeded those of female patients in all ages, with a decrease in Z-scores in male patients during puberty and overlapping CIs from the age of 15 years.

The aortic root growth was not significantly different between HI-*FBN1* and DN-*FBN1* mutation carriers (p=0.313) (figure 4). However, aortic root size was larger in patients with MFS with DN-*FBN1* variants, resulting in a loss of cysteine content than in patients with MFS with variants not affecting the cysteine content or resulting in a gain of cysteine content (figure 5).

Surgical replacement of the aortic root in patients with MFS

Eleven patients with MFS underwent aortic root surgery at a mean age of 16.5±1.8 years and with an average aortic

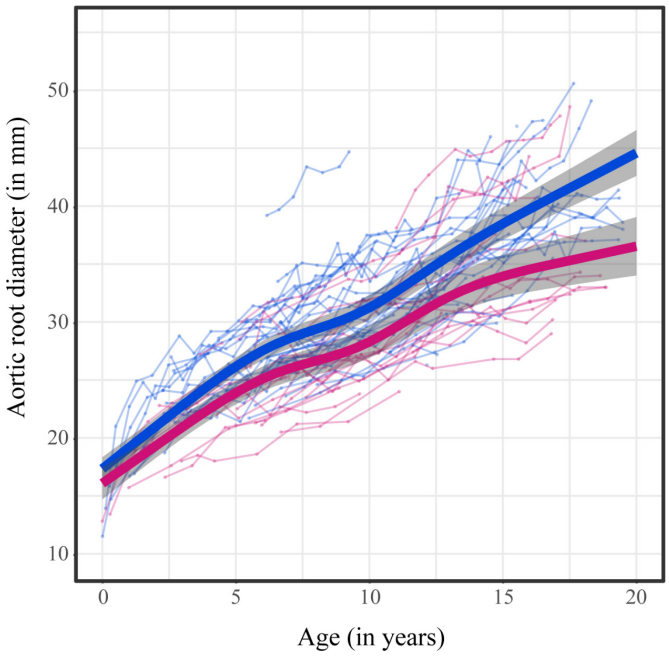

Figure 2 Individual and average aortic root diameters (in mm) in 61 male patients with Marfan syndrome (blue) and 36 female patients with Marfan syndrome (pink); 95% CIs are depicted (grey area).

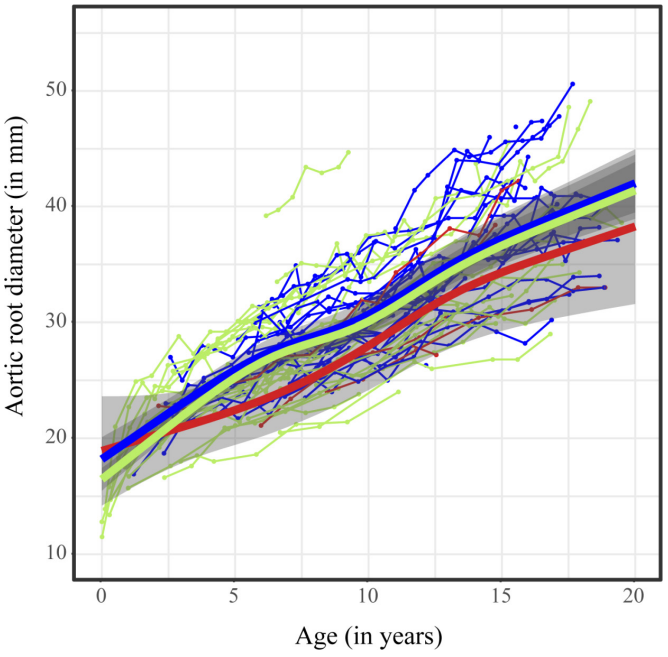

Figure 4 Individual and average aortic root diameter (in mm) in 55 children with DN-*FBN1* variants (green), 37 children with HI-*FBN1* variants (blue) and 5 children with an unknown *FBN1* variant or unclassifiable *FBN1* variant (red); 95% CIs are depicted (grey area).

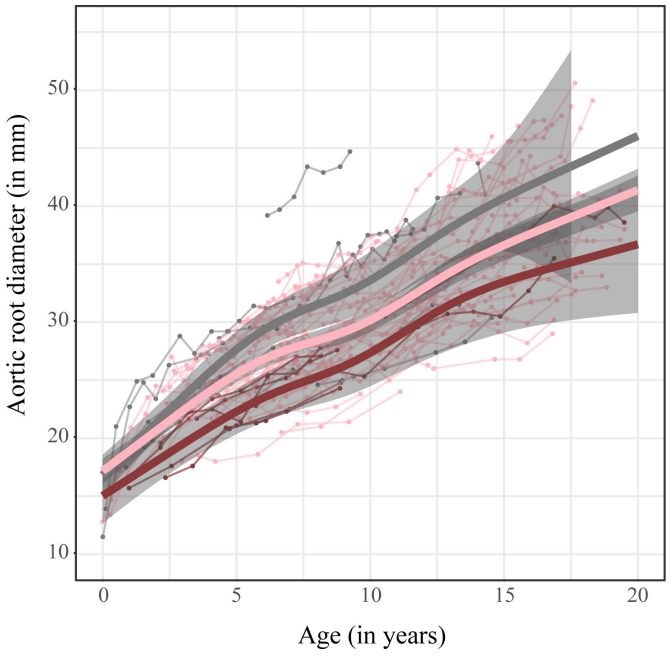

Figure 5 Individual and average aortic root diameter (in mm) of 55 children with DN-*FBN1* variants resulting in a loss of cysteine content (15 children, grey), gain of cysteine content (9 children, red) or not affecting the cysteine content (31 children, pink); 95% CIs are depicted (grey area). Due to the lack of data about aortic root growth in DN-*FBN1* variants resulting in a loss of cysteine content in older children, the 95% CI between the ages of 17.5 and 20.0 years becomes extremely large.

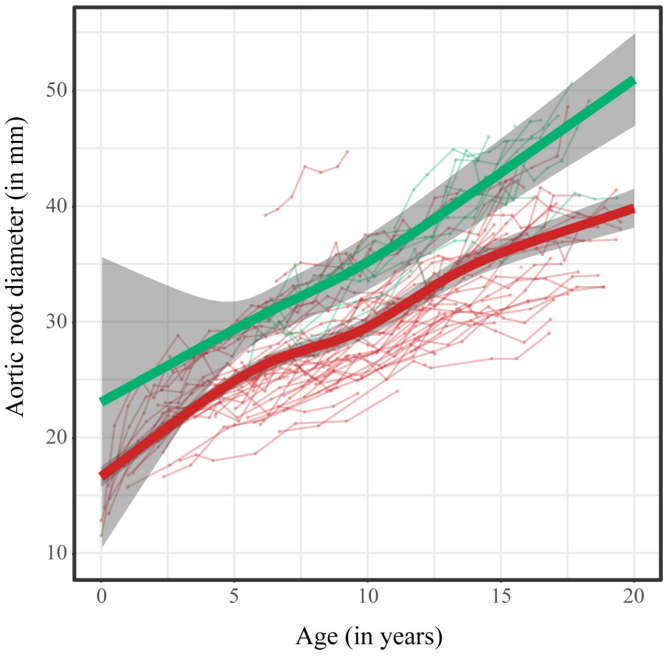

Figure 6 Individual and average aortic root diameter (in mm) in patients with Marfan syndrome who underwent an aortic root replacement (green) and patients with Marfan syndrome who did not (red); 95% CIs are shown (grey area).

root diameter of 45.6±3.3 mm (range in Z-scores: +1.20 to +5.63), all of which were uncomplicated prophylactic David procedures. There were more surgical replacements in male patients (n=8, Z-scores +2.06 to +5.63) than female patients (n=3, Z-scores +1.20 to +4.52). No aortic dissections nor deaths occurred during follow-up. Figure 6 gives insight into the aortic root growth of the patients with MFS, who underwent an aortic root replacement versus those who did not require aortic root surgery. From an early age, the children with MFS who required prophylactic surgery had a significantly greater aortic root diameter compared with the patients with MFS who did not require aortic root surgery.

DISCUSSION

This study presents clinically useful, longitudinal aortic root growth charts of patients with MFS aged 0–20 years. In addition, we had four major findings: (1) from the age of 8 years, aortic root growth further accelerates in patients with MFS compared with control subjects; (2) in patients with MFS, there is a significant difference in absolute aortic root diameter between male and female patients. These differences are largely explained by differences in height; (3) in patients with MFS, aortic root growth does not differ between HI-*FBN1* and DN-*FBN1* mutation carriers. However, considering only patients with MFS with DN-*FBN1* variants resulting in loss of cysteine content, we observed a more severe phenotype with larger aortic root diameters; and (4) patients with MFS who underwent prophylactic aortic root surgery during childhood could be identified at a very early age by their absolute aortic root diameter.

Aortic root growth in children and adolescents with MFS

This is the first study presenting longitudinal data on aortic root growth in children and young adults with MFS. Our study included all patients with MFS attending our outpatient clinic, regardless of aortic root size. Although aortic root size is dilated by definition in a subset of patients, our data provide new insight in absolute aortic root growth patterns from a very early age. As expected, the average aortic root diameter was significantly larger in children with MFS than in the healthy subjects at all ages. In addition to this, our data show that from the age of 8 years, the difference in aortic root diameter between patients with MFS and control subjects becomes more pronounced due to accelerated growth of the absolute aortic root in patients with MFS. This finding may provide some insight into the mechanism of aortic root dilatation in children with MFS. It has previously been suggested that in patients with MFS, as a result of aortic root dilation, increased aortic wall stress, in turn, leads to accelerated aortic root dilatation.[21] Our results show that, although aortic dilation is present from a very early age, the aortic growth pattern remains parallel to that of healthy children during the first 8 years of life. Accordingly, this mechanism of accelerated root growth due to increased aortic wall stress may not play a role in the first decade of life. More research is needed to determine the

underlying mechanisms leading to increased aortic root diameters very early in life.

Influence of sex and height on aortic root diameter growth

Male patients with MFS had a significantly larger absolute aortic root diameter as well as larger aortic root Z-scores than female patients with MFS at all ages. The absolute difference in aortic root diameter between male and female patients increased during puberty. As can be seen in figure 3, this sex difference in aortic root size is largely explained by patient length. Earlier studies in healthy children found conflicting results regarding sex-related differences in aortic root diameter.[2 22 23] However, studies in healthy adults reported an association between larger aortic root diameter and male sex, even after correcting for age, height and weight.[23 24] The exact relation between sex, age and height on aortic root growth, therefore, remains a matter of debate and warrant future investigation.

Our finding regarding larger aortic root diameter among male patients with MFS compared with female patients with MFS and the influence of height has important clinical relevance. Current clinical management of patients with MFS uses BSA (thus taking into account height) and sex to calculate Z-scores, which guide follow-up frequency and use of antihypertensive medication. However, surgical cut-off points are still based on absolute diameters with no differentiation for sex nor Z-scores. From previous data, we know that adult female patients with MFS just below the surgical threshold are at increased risk of type A dissections.[25 26] In a cohort analysed by Meijboom *et al*,[26] 33% of all type A dissections in adult female patients with MFS could have been prevented by lowering the threshold for aortic root replacement by 5 mm. As can be observed from figure 2, female patients reaching the absolute cut-off points of 45–50 mm are indeed much more deviated from their predicted absolute aortic root diameter than male patients; that is, tall female patients with accordingly large aortic root size represent a worse phenotype than male patients of the same length and aortic root size. The aforementioned studies, in combination with our data, underline the importance of further research on sex-differentiated thresholds for surgical intervention

HI-FBN1 mutations versus DN-FBN1 mutations

In our cohort of young patients with MFS, the average aortic root growth was not significantly different among patients with MFS with HI-*FBN1* variants compared to those with DN-*FBN1* variants. Previous research in adult patients with MFS showed an important difference in aortic root diameters among HI-*FBN1* mutations versus DN-*FBN1* mutations, with larger aortic root diameters in patients with MFS with pathogenic HI-*FBN1* variants. Moreover, adults with HI-*FBN1* mutations were demonstrated to have a 1.6-fold increased risk (HR 1.6, 95% CI 1.1 to 2.2, p=0.005) of aortic complications (eg, aortic dissection, cardiovascular mortality and aortic surgery) compared with adults with a DN-*FBN1* mutation.[13] The underlying mechanism for this observation is still unclear. Earlier research indicated that not the production of a mutant *FBN1* protein but the decreased production of a normally functioning *FBN1* protein is the main determinant for failed microfibrillar assembly.[27] In addition, lower levels of *FBN1* protein were associated with larger aortic root diameters and increased risk of cardiovascular complications.[28 29] However, recent research showed that there is a subgroup of pathogenic DN-*FBN1* variants (affecting or creating cysteine residues and in-frame deletions in the cb-EGF domains of exons 25–36 and 43–49), which resulted in an increased risk of cardiovascular complications, comparable with even more deleterious than seen in patients with pathogenic HI-*FBN1* variants. In this subgroup, the cardiovascular complications occur earlier in life compared with patients with MFS with HI-*FBN1* mutations or 'other' DN-*FBN1* mutations.[15] In another study, DN-*FBN1* variants resulting in a loss of cysteine content were also associated with a worse cardiovascular phenotype.[16] The results of our subgroup analysis support these observations. In children with MFS and DN-*FBN1* variants resulting in a loss of cysteine content, larger aortic root diameters were observed. This observation points towards an important genotype–phenotype association among patients with MFS with cysteine affecting variants. In addition, this observation may explain why our results showed no difference between HI-*FBN1* and DN-*FBN1* variants in aortic root growth. In our study, approximately 10% of children with MFS required an aortic root replacement at a young age. These patients may be excluded in studies on aortic root growth in adults, possibly affecting the studied genetic variants on MFS in adults with regard to aortic root growth. More research is necessary to elucidate the relationship between *FBN1* genotype and severity of the aortopathy.

Aortic root replacement during childhood

Patients with MFS requiring an aortic root replacement before the age of 20 years had a significantly larger aortic root diameter from a very early age compared with patients with MFS who did not. This finding suggests that the moment of surgical intervention can roughly be determined by measuring the aortic root diameter in early childhood. This observation is in accordance with previous observations in paediatric patients with MFS, concluding that larger baseline dimensions of the aortic root predict progressive aortic root dilatation later in life.[6 7 30–33] Using absolute aortic root diameters, this study provides clinically useful growth charts, allowing to stratify individual patients at a glance according to their future perspective of aortic root dilatation. This is of great benefit for counselling young patients with MFS and their caregivers and for clinical decision making with regard to follow-up and prophylactic treatment.

Limitations

The current study has the inherent limitation of being a retrospective study. A complete set of echocardiographic examinations from birth to 20 years was not available in all patients due to differences in the age of presentation and follow-up intervals. Part of the control group had minor cardiac abnormalities; therefore, small differences in aortic root growth compared with healthy children cannot be ruled out.

Furthermore, inherent to our study design, the difference in aortic root diameter between patients with MFS with and without aortic root replacement before the age of 20 years may have been underestimated, since some of the patients did not meet the criteria for aortic root surgery at the time of inclusion but may meet these criteria before reaching the age of 20 years. These patients were now included in the 'no surgery' group, possibly increasing the average aortic root diameter in that group.

In addition, selection bias based on MFS diagnosis cannot be ruled out. Diagnosing MFS in young children is challenging in case of a positive family history of MFS or presence of a *FBN1* mutation, without other clinical characteristics of MFS (eg, ectopia lentis, aortic root dilatation Z-score of ≥3 or systemic score of ≥7). These clinical characteristics take time to develop and can therefore not be present in young children with MFS. Therefore, children with MFS could possibly have been excluded from our study cohort since one of these three phenomena was not yet present.

Finally, the effect of medication on aortic root growth could not be evaluated due to the retrospective nature of the study. Of the patients with MFS, 46 (47%) children received medication (atenolol, losartan or both) during follow-up. According to the current guidelines, patients with higher Z-scores were more likely to receive prophylactic medication, which could have reduced the aortic root dilatation rate.

Future perspective

As can be easily appreciated from our growth charts, great heterogeneity exists among the severity of aortic dilation and growth between patients. In order to further tailor predictions of aortic root growth in individual patients, more research with larger sample sizes is needed. In addition, more research in needed on the various factors that have been identified to influence aortic root growth, such as patient height, sex, genotype–phenotype correlations, as well as studies that take in to account wall stress, wall shear stress and aortic stiffness.

CONCLUSIONS

The present study provides clinically useful, longitudinal growth charts on aortic root growth in children and adolescents with MFS. These growth charts indicate that the difference in aortic root diameter between patients with MFS and healthy control subjects becomes more pronounced from the age of 8 years. Furthermore, the study shows that young patients with MFS needing prophylactic aortic root surgery can be identified at a very young age. Accordingly, our growth charts can help clinicians in decision making with regard to counselling follow-up and prophylactic therapy. In addition, our growth charts show important differences in absolute aortic root diameters between male and female patients which, although closely related to height, underline the importance of further research on sex-differentiated thresholds for surgical intervention. Finally, no differences in aortic root growth are observed among HI-*FBN1* mutation and DN-F*BN1* mutation carriers during childhood. However, DN-*FBN1* variants resulting in loss of cysteine content showed a more severe phenotype.

Acknowledgements We thank Vivian de Waard for her critical review of this article.

Contributors Concept and design of the study: EvE, ASV and AEvdH. Acquisition and analysis of the data: EvE, AEvdH, ACPMB and RB. Statistical analysis: ASV and EvE. Drafting of the manuscript: EvE, ASV and AEvdH. Interpretation of the data and critical revision of the manuscript: all authors. EvE and AEvdH accept full resonsibility for the the work and/or conduct of the study, had access to the data, and controlled the desicion to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The local committee for medical ethics of both centres approved the study and waived the need for informed consent (medical ethics review committee of the Academic Medical Center, reference number W19_088#19.117, and medical research ethics committee of Leiden, The Hague Delft, reference number: G19.104).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data underlying this article are available from the corresponding author upon reasonable request.

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