Skeletal evolution in Marfan syndrome: growth curves from a French national cohort

Grégoire Benoist¹, Florence Tubach¹, Carine Roy¹, Sabine Rioux¹, Marlène Michelon-Jouneaux¹, Bertrand Chevallier¹, Guillaume Jondeau¹ and Chantal Stheneur¹

BACKGROUND: To describe the growth patterns of children affected by Marfan syndrome (MFS) compared with those of unaffected children and to create growth charts.

METHODS: An observational study of children referred to the French National MFS Reference Centre. A total of 259 children carrying an *FBN1* gene mutation and fulfilling Ghent 1 criteria (MFS group) and 474 mutation-negative sibling controls (non-MFS group) were evaluated. Both groups were compared with French-accepted reference nomograms (Reference group).

RESULTS: Boys and girls from the MFS group were significantly taller than those in the non-MFS group and in the reference group at all ages ($P < 0.0001$). But, MFS children's overgrowth reduced with age. At 17 years of age, the mean height (MFS vs. non-MFS) was 191.2 ± 8.4 cm ($+2.9$ SD) vs. 182.9 ± 8.1 ($+1.6$ SD) for boys and 178.3 ± 7.6 cm ($+2.7$ SD) vs. 169.5 ± 6.8 ($+1.2$ SD) for girls, respectively. By contrast, the mean BMI of children in the MFS group was similar to those in the non-MFS group and inferior to the values of French general population, evolving around -1 SD.

CONCLUSION: Growth patterns differ in patients with an *FBN1* mutation. Knowing the growth parameters should allow physicians to better counsel patients and detect the associated diseases. The provided curves could also help to predict the final height.

Marfan syndrome (MFS) (MIM 154700) is a connective tissue disorder with autosomal-dominant inheritance caused mostly by a mutation in the *FBN1* gene (1). The prevalence of that disease is estimated at two or three cases per 10,000 individuals (2). MFS is characterized by a broad range of clinical manifestations involving the skeletal, ocular, cardiovascular, integument, pulmonary, and central nervous systems with great phenotypic variability (2–4). Cardiovascular involvement in the form of aortic aneurysm or a dissecting aorta is the most serious life-threatening aspect of the syndrome. The succession of classifications (Berlin, Ghent 1, and Ghent 2) illustrates the complexity of diagnosis, explaining the growing importance of genetic testing (5). In children, diagnosis is even more difficult because many

manifestations are age-dependent and are therefore not yet present; so, the classification criteria are lacking the sensitivity (3). However, familial screening, facilitated by molecular biology testing, now allows early recognition of children with more limited clinical features.

Tall stature is a frequent reason to suspect MFS and to refer a child for evaluation, even though height is not part of any current international classification. It is further clinically relevant, as tall stature may also influence the functional outcome of children (6), and questions about the final height from families or MFS adolescents are recurrent in an external clinic. Pyeritz *et al.* (7) and Erkula *et al.* (8) have already proposed growth charts for American children with MFS, based on a retrospective review of MFS patients diagnosed on a clinical basis. In addition, growth charts for Korean children with MFS have recently been developed (9). However, growth of American or Asian children differs from that of European children, thereby making it important to have growth charts developed from a European sample of MFS children (10,11).

The molecular defect may be of importance in the determination of height in patients. Specifically, patients carrying *TGFBR2* mutations have a lower mean height than patients carrying an *FBN1* mutation (12); this aspect was not taken into account in previous studies. Therefore, our study aims to describe the growth pattern (height, weight, BMI, and arm-span-to-height ratio) of French children with MFS carrying an *FBN1* mutation in modern care, so as to provide updated special charts for MFS indicating the height according to age and gender.

METHODS

Patients and Methods

All subjects under 18 years of age who came to our multidisciplinary consultation at Bichat Hospital in Paris (CNR Marfan: Centre National de Référence pour le syndrome de Marfan et apparentés) between 1995 and 2010 were considered for this study. Children came to our clinic either because Marfan syndrome was suspected by a physician or the patient himself, or because children were relatives of MFS patients (familial screening is systematic in our clinic). During consultation, all children underwent an exhaustive clinical evaluation, including screening for features belonging to Ghent 1 criteria. Follow-up visits (yearly visits between 1995 and 2001 and a visit every 2 years thereafter), involving the same assessment, were

¹Department of Pediatrics, Ambroise Paré Hospital, APHP, Boulogne-Billancourt, France. Correspondence: Chantal Stheneur (chantal.stheneur@apr.aphp.fr)

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Table 1. Comparison of skeletal features in children from the MFS group (left) and the non-MFS group (right) in each age group

	Marfan group										Non-Marfan group				
	Total N = 259	P-value MFS/ non-MFS	0–6 years N = 103	P-value MFS/ non-MFS	7–9 years N = 101	P-value MFS/ non-MFS	10–14 Years N = 137	P-value MFS/ non-MFS	15–17 Years N = 114	P-value MFS/ non-MFS	Total N = 422	0–6 Years N = 97	7–9 Years N = 68	10–14 Years N = 138	15–17 Years N = 162
Height (cm) mean ± SD	144.9 ± 29.8 (N = 259)	0.0007	114.4 ± 13.9 (N = 98)	NS	141.5 ± 9.0 (N = 100)	<0.0001	163.5 ± 11.0 (N = 135)	0.009	182.7 ± 10.8 (N = 107)	<0.0001	152.7 ± 27.6 (N = 400)	111.4 ± 13.0 (N = 83)	135.6 ± 9.3 (N = 67)	159.7 ± 12.0 (N = 126)	177.2 ± 9.3 (N = 159)
Height (SD for age)	3.6 ± 1.8 (N = 252)	<0.0001	4.2 ± 2.0 (N = 98)	<0.0001	3.9 ± 1.5 (N = 100)	<0.0001	3.6 ± 1.6 (N = 135)	<0.0001	2.6 ± 1.4 (N = 107)	<0.0001	1.9 ± 1.5 (N = 400)	2.4 ± 2.0 (N = 83)	2.2 ± 1.6 (N = 67)	1.9 ± 1.2 (N = 126)	1.5 ± 1.2 (N = 159)
Weight (kg) mean ± SD	35.9 ± 19.3 (N = 236)	<0.0001	19.1 ± 5.0 (N = 93)	NS	29.7 ± 7.7 (N = 95)	NS	44.4 ± 12.2 (N = 127)	NS	62.3 ± 12.9 (N = 103)	NS	42.7 ± 18.4 (N = 367)	19.9 ± 5.0 (N = 77)	29.8 ± 7.3 (N = 63)	45.4 ± 12.3 (N = 113)	60.6 ± 10.6 (N = 144)
BMI (kg/m ²) mean ± SD	15.8 ± 3.1 (N = 236)	<0.0001	14.4 ± 1.7 (N = 93)	<0.0001	14.7 ± 2.4 (N = 95)	0.0018	16.4 ± 3.0 (N = 127)	0.0031	18.5 ± 3.2 (N = 103)	0.04	17.4 ± 3.1 (N = 367)	15.7 ± 2.2 (N = 77)	16.0 ± 2.9 (N = 63)	17.6 ± 3.2 (N = 113)	19.3 ± 2.9 (N = 144)
Arm/height mean ± SD	1.03 ± 0.03 (N = 245)	<0.0001	1.02 ± 0.03 (N = 93)	<0.0001	1.03 ± 0.04 (N = 73)	<0.0001	1.04 ± 0.03 (N = 108)	<0.0001	1.04 ± 0.03 (N = 64)	0.0012	1.02 ± 0.03 (N = 362)	1.00 ± 0.04 (N = 70)	1.00 ± 0.02 (N = 60)	1.02 ± 0.03 (N = 106)	1.03 ± 0.03 (N = 136)
Arm/ height > 1.05	29.4% (N = 245)	<0.0001	14.0% (N = 93)	NS	21.9% (N = 73)	0.0018	37.0% (N = 108)	<0.0001	46.2% (N = 65)	<0.0001	11.4% (N = 362)	5.6% (N = 72)	3.3% (N = 60)	12.8% (N = 125)	15.7% (N = 166)
Scoliosis angle (°) mean ± SD	9.9 ± 11.2 (N = 154)	0.0009	5.7 ± 6.6 (N = 50)	0.0008	9.2 ± 7.7 (N = 61)	<0.0001	11.0 ± 9.9 (N = 83)	<0.0001	15.6 ± 13.3 (N = 61)	<0.0001	5.3 ± 5.8 (N = 297)	2.7 ± 1.4 (N = 61)	4.2 ± 3.9 (N = 41)	5.0 ± 6.0 (N = 98)	6.9 ± 6.6 (N = 122)
Scoliosis angle > 10°	33.8% (52/154)	0.010	16.0% (8/50)	0.01	29.5% (18/61)	0.007	41.0% (34/83)	<0.0001	59.0% (36/61)	<0.0001	12.5% (37/297)	1.6% (1/61)	7.3% (3/41)	10.2% (10/98)	19.7% (24/122)

MFS, Marfan syndrome; NS, nonsignificant.

proposed when MFS was diagnosed or could not be ruled out. Height was determined by placing the children with their backs against a wall, looking straight ahead, and with their arms hanging freely at their sides. Weight was obtained using electronic scales to the nearest 0.1 kg; the children wore light clothing and no shoes. Arm span was measured from the tip of the third digit of the right hand to the third digit of the left hand, including the shoulder width; the children stood with arms stretched perpendicular to the body. The initiation of puberty was defined by the increase of the upper testicular volume to 4 ml for boys (G2), and the development of breast buds for girls (S2). The bone age was compared with the atlas of Greulich and Pyle (13) during consultation.

Molecular biology (screening for an *FBN1* mutation) was performed in the case of high clinical suspicion of MFS (the presence of at least one major and one minor Ghent 1 criteria) or the existence of a known mutation in the family.

Only families with an *FBN1* mutation were considered for this study. Children carrying an *FBN1* mutation who fulfilled the Ghent 1 criteria during follow-up were included in the “MFS group”. Unaffected children (a mutation-negative sibling only) were included

in the “non-MFS group” in order to get a modern nonselected control group. Any patient who had received a hormonal treatment for overgrowth was excluded (eight patients). All parents signed an informed consent form.

Statistical Analysis

The characteristics of children are reported by age stratum at consultation: 0–6 years old, 7–9 years old, 10–14 years old, and 15–17 years old. Each child could contribute to more than one age stratum, but only once per age stratum (first visit during this stratum). These characteristics are expressed by frequencies and percentages for categorical variables, and by means and SD for continuous variables. Comparisons between children with MFS and those without MFS were performed in each stratum of age for categorical variables using chi-square or Fisher's exact test, and for continuous variables, Student's *t*-test or Wilcoxon's rank-sum test was conducted, as appropriate. Proband children were compared with non-proband children using the same statistical tests. The significance level was 5%.

Figure 1. MFS charts of body length according to age and gender (**a** boys, **b** Girls) for MFS children carrying an *FBN1* mutation (mean, ± 1 SD, ± 2 SD). The curves in boxes represent the delta of centimeters vs. age between the MFS group and the French general population (Sempe curves).

The receiver-operating characteristic (ROC) curve and the Youden index (maximum potential effectiveness of a continuous data) were used to evaluate the best cut point for an arm-span-over-height ratio at different ages.

The height of boys and girls was plotted against the chronological age at 1-year intervals to compare the growth between children with MFS and those without MFS. Curves were smoothed (14), and the French reference growth curves from Sempe were added to the graphs for comparison (15). Sempe curves were chosen as they are still widely used in France; however, we also compared the data with the WHO curves. The average difference between the growth curve of children with MFS and the Sempe growth curve was plotted against their age.

Statistical analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS

Population

The MFS group consisted of 259 children (134 boys) (fulfilling Ghent 1 criteria and carrying an *FBN1* mutation) with 850 visits (419 for boys and 431 for girls). The non-MFS group was made up of 422 children with 512 visits (278 boys) (Table 1).

Clinical Presentation

MFS group. A number of 103 (39.8%) patients came for the first visit between the age of 0 and 6 years old, 49 (18.9%) between 7 and 9 years old, 68 (26.2%) between 10 and 14 years old, and 39 (15.1%) between 15 and 17 years old. A family history of MFS was present in 158 (61.0%) children.

Non-MFS group. Non-MFS group children were older at the first visit (11.1 ± 4.7 vs. 8.6 ± 4.6 years old; $P < 0.0001$). By contrast, the sex ratio was similar in the two groups (1.2 vs. 1.1 (nonsignificant)).

Statural Growth

Growth curves of boys and girls with MFS were plotted with the mean and standard deviations ($\pm 1, \pm 2$) in Figure 1. In centimeters, the difference in height between children with MFS and the French reference increased until 13 years old in boys and 12 years old in girls, and then decreased (Figure 1, boxes). Assessed by standard deviation, boys in the MFS group's overgrowth reduced with age from +4.2 SD between 0 and 6 years old, to +2.7 SD between 15 and 17 years old (Table 1 and Figure 2). Therefore, a prediction at the age of 10 could lead to an overestimation of the final height by more than 8 cm. For girls in the MFS group, the difference also decreased from +3.9 SD between 0 and 6 years old, to +2.5 SD between 15 and 17 years old. At 17 years of age, the mean height of the boys in the MFS group was 191.2 ± 8.4 cm ($+2.9$ SD) vs. 182.9 ± 8.1 cm ($+1.6$ SD) in the non-MFS group and 178.3 ± 7.6 cm ($+2.7$ SD) for girls in the MFS group vs. 169.5 ± 6.8 cm ($+1.2$ SD) in the non-MFS group.

In probands, height was greater only in males at 10–14 years (4.4 ± 1.2 SD above the Sempe mean vs. 3.5 ± 1.7 in non-probands) ($P = 0.04$) and 15–17 years (3.2 ± 1.2 SD above the Sempe mean vs. 2.4 ± 1.5) ($P = 0.02$).

Figure 2. Reduction of overgrowth (expressed in SD) in MFS children in different age groups.

A comparison of children from the MFS group and children from the non-MFS group showed that boys and girls from the MFS group were significantly taller than boys and girls from the non-MFS group (Figure 3). But expressed in SD, the height difference between the two populations decreased from +1.6 SD in the 0–6-year-old group to +1.1 SD in the 15–17-year-old group.

BMI

In our MFS population, BMI increased slightly throughout the growth phase from 14.4 ± 1.7 (-1 SD) to 18.5 ± 3.2 kg/m² (-0.5 SD). The difference between the two groups (MFS vs. non-MFS) decreased significantly with age. In the 0–6-year-old section, the BMI difference between the MFS and non-MFS group was 1.3 kg/m² (< 0.0001) and 0.8 kg/m², respectively, in the 15–17-year-old section ($P = 0.04$).

Arm-Span-Over-Height Ratio and Scoliosis

The mean value for the arm-span-over-height ratio was 1.03 ± 0.03 for children in the MFS group, but increased from 1.02 ± 0.03 when 0–6 years old to 1.04 ± 0.03 when 15–17 years old. The percentage of children in the MFS group with a ratio ≥ 1.05 increased accordingly in each age group from 14% when 0–6 years old; 21.9% when 7–9 years old; 37.0% when 10–14 years old; and to 46.2% when 15–17 years old, illustrating the altered sensitivity of skeletal criteria in young children. A comparison between children from the MFS and non-MFS groups showed that the mean arm-span-to-height ratio was significantly greater in those with MFS than those without MFS (Table 1; $P < 0.0001$) for the whole population and in each age group. Also, the percentage of non-MFS group children with a ratio > 1.05 remained significantly lower than the percentage in children with MFS in all age groups even if it increased with age. Using ROC curves, the maximum Youden index found a value of 1.03 for the whole population, evolving from 1.00 for 0–6 years old; 1.02 for 7–9 years old; 1.04 for 10–14 years old; and to 1.05 for 15–17 years old children. By grouping

Figure 3. Body length (cm) vs. age (years) for male (a) or female (b) children with MFS carrying an *FBN1* mutation (black curves), or unaffected parents (control, gray curves) plotted on the graph with the French general population (plain thin lines for the mean and dotted lines for ± 2 SD) as determined by Sempe.

the first two classes (0–9 years old), the maximum Youden index was 1.01 (sensitivity = 0.65, specificity = 0.65).

The mean angle for scoliosis increased from $5.7 \pm 6.6^\circ$ to $15.6 \pm 13.3^\circ$ in MFS children. Compared with the non-MFS group, the angle for scoliosis was significantly greater in each age section in MFS groups (Table 1). When a cutoff of 10° was chosen, the prevalence of a scoliosis was 10 times more frequent in children aged 0–6 years old (16.0% vs. 1.6%); this ratio decreased progressively with age to a ratio of 3 at the age of 15–17 years old (59.0% vs. 19.7%). When a cutoff of 20° was chosen (as suggested in the most recent Ghent 2 criteria), none of the non-MFS group children under 10 years old had positive scoliosis. The prevalence of scoliosis was 6.3 times

higher in the MFS group children aged 10–14 years and similarly decreased to a ratio of 3.2 at the age of 15–17 years.

Puberty Onset

Puberty onset occurred significantly earlier in girls from the MFS group when compared with girls from the non-MFS group (10.4 ± 1.6 years vs. 11.5 ± 1.2 years; $P = 0.04$). No differences were observed in the boys, but this may have been due to lack of power (less data available for boys).

DISCUSSION

Our study provides, for the first time, standards for height, weight, BMI, and arm span in children (boys and girls)

carrying an *FBN1* mutation and fulfilling Ghent 1 criteria. Previous studies have reported the growth pattern of children with a diagnosis of Marfan syndrome based on clinical grounds. This could be a major limitation as the clinical features of MFS appear with age, meaning that clinical diagnosis likely selects the more severe patients. Furthermore, the reason for referral (often skeletal features in our experience) may bias the sample selected, and deriving growth charts from a selected population may be of concern when making growth predictions in an unselected population (7–9).

One of the reasons for the inclusion of the Sempe curve is that currently in France, it is a more frequently used growth chart. A very recent French study (11) containing the data of 82,151 measurements available for 27,257 children in different age groups from birth to 18 years shows that the current French population of children was on average 0.5 standard deviations taller than the French reference population and was in fact closer to the WHO growth charts, except for girls after 15 years of age. In addition, the overgrowth present with MFS decreases with puberty when expressed in SD with both the Sempe curves and the WHO curves. The mean height that we report for our control group is +1.2 SD for girls and +1.6 SD for boys. We cannot explain the overgrowth of the non-affected sibling. Further studies would be interesting to confirm these data in mutation-negative siblings.

Interestingly, the final height of males with MFS is almost identical in different countries: 191.2 ± 8.4 cm in France, 191.4 ± 5.2 cm in Korea (9), and 191.3 ± 9.0 cm (8) in the United States. This is true despite the difference in men's final height in each general population (174.4 vs. 173.3 and 176.7 cm, respectively), suggesting that the presence of Marfan syndrome results in a similar height, regardless of the geographic origin or the genetic background. By contrast, the final height of females with MFS differs according to the country: 178.3 ± 7.6 cm in France, 176.2 ± 5.3 cm in Korea, and 175.4 ± 8.2 cm in the United States; in the general population, the final height in females is 162.5, 160.7, and 163.1 cm, respectively. The reason for this observation is unclear.

Although an observational and retrospective study, data were collected prospectively, and measures were standardized and obtained by pediatricians with extensive experience treating this pathology. All patients seen in the Marfan CNMR were included in the register if they belong to a family with an *FBN1* mutation and meet the criteria. The familial screening is systematic in our clinic, and therefore should minimize the selection bias toward severity that can be observed when probands are overrepresented. This is illustrated by the fact that children with MFS were taller and presented a greater arm-span-over-height ratio. The results are therefore relevant to practice in the general population.

As it is now possible to propose treatments to limit the height in children when the predicted adult height is excessive, the ability to reliably determine the final height is

important. In France, such a treatment is proposed if the final height exceeds 185 cm for girls and 200 cm for boys according to a regulatory agency (16). The normograms reported in this study could be used to predict growth, an adult's height, and make an appropriate decision on the use of a growth limitation therapy in patients with an *FBN1* mutation.

Usually, the representation of a patient with MFS is an extremely lean person. However, in our study, the mean BMI value evolves from -1 SD to -0.5 SD, indicating that a low BMI may not be as severe as expected in the MFS population except perhaps in younger patients.

Lastly, we report the arm-span-over-height ratio throughout childhood. In the general population, the arm-span-over-height ratio that tends to increase with age during childhood, is higher in boys than in girls, and remains around a mean value of 1.00 ± 0.02 (17,18). Our results are in accordance with the previous studies (1,19–21) reporting that, in the MFS population, this ratio is significantly higher than that in the non-MFS population; however, evolution with age is similar. Therefore, the cutoff ratio should be adapted with age, and we propose that before the age of 10 years, the arm-span-over-height ratio should be considered as a diagnostic criterion for MFS when it is >1.01 .

Our study has some limitations. Including only *FBN1* mutation carriers fulfilling Ghent 1 criteria may not completely preclude a bias toward more severe cases of *FBN1* mutation, as the milder forms may remain unrecognized; however, this is limited by the systematic familial screening performed in our center, including mutation screening. We decided to keep children with scoliosis for the analysis of height, and not adjust the height values with the use of correction equations as proposed by some (22). In fact, scoliosis may decrease the height and may have attenuated the difference between MFS and non-MFS populations.

We integrated our data with “visits” as the unit. We used both repeated data for each child (as in a longitudinal study) and several examinations of different subjects in the same age group (as in a cross-sectional study). A longitudinal prospective study with a larger group, a single observer, and the same equipment, would have been optimal, but due to time constraints and practical limitations, it is not feasible. All the growth information was collected in our center, which explains why the data are scarcer at the extremes of curves (for example, length at birth because of the age for diagnosis).

CONCLUSION

The charts generated in this study for MFS patients carrying an *FBN1* mutation can be useful for pediatricians to appreciate growth in these children as precisely as that in unaffected children, to predict a final height, monitor growth-reducing therapy, and even screen a suspected case for MFS. The physical symptoms, particularly the height, are a major source of psychological suffering in MFS (6); reassuring parents and children regarding what to expect can help them to better cope with their illness.

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