Sanfilippo disease (mucopolysaccharidosis type III): Early diagnosis and treatment

de Ruijter, J.

Citation for published version (APA):
SEVEN
GROWTH IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS TYPE III (SANFILIPPO DISEASE)

Jessica de Ruijter¹, Lianne Broere¹, Margot F. Mulder², Ans T. van der Ploeg³, M. Estela Rubio-Gozalbo⁴, Saskia B. Wortmann⁵, Gepke Visser⁶, Frits A. Wijburg¹

¹Department of Pediatrics and Amsterdam Lysosome Centre ‘Sphinx’, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; ²Section of Metabolic Diseases, Department of Paediatrics, VU University Medical Center, Amsterdam, The Netherlands; ³Center for Lysosomal and Metabolic Diseases, Department of Paediatrics, Erasmus Medical Center, Rotterdam, The Netherlands; ⁴Department of Pediatrics and Laboratory of Genetic-Metabolic Diseases, Maastricht University Medical Center, Maastricht, The Netherlands; ⁵Department of Pediatrics, Institute for Genetic and Metabolic Disease, Radboud University Nijmegen Medical Center, The Netherlands; ⁶Department of Metabolic and Endocrine Diseases, Wilhelmina Children’s Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Submitted
ABSTRACT

Background: Mucopolysaccharidosis III (Sanfilippo disease) is a lysosomal storage disorder mainly characterized by progressive neurodegeneration with cognitive decline and relatively attenuated somatic signs and symptoms. Although short stature is invariably present in patients with the other mucopolysaccharidoses, it has not been sufficiently addressed in MPS III. The aim of this study was to investigate growth data of a large Dutch MPS III cohort in order to construct growth charts for MPS III patients.

Methods: Height, weight, head circumference (HC) and body mass index (BMI) data from 118 MPS III patients were used to construct reference curves, using the lambda, mu, sigma (LMS) method. Genotype-group comparisons for height standard deviation scores (SDS) were performed by Kruskal-Wallis analysis for different age-groups.

Results: Birth weight and length were within normal ranges for gestational age and showed a significantly stunted growth from age 6 years onwards. Mean final heights were 169.7 cm (-2.0 SDS) and 165.4 cm (-0.84 SDS) for adult males and females, respectively. Phenotypic severity, as assessed by genotyping, correlated with growth pattern and final height. In addition, mean BMI and HC SDS were significantly higher when compared to Dutch standards for both boys and girls.

Conclusions: Growth in MPS III is stunted mainly in patients with the severe phenotype. We provide disease specific growth references that can be used for clinical management of MPS III patients and may be of value for future treatment studies.
INTRODUCTION

Mucopolysaccharidosis type III (Sanfilippo disease, MPS III; OMIM #252900, 252920, 252930, 252940) is a rare autosomal recessive disorder primarily characterized by progressive neurodegeneration, which affects approximately 1 in 50,000 newborns. MPS III belongs to the mucopolysaccharidoses, a group of lysosomal storage disorders caused by deficient breakdown of glycosaminoglycans (GAGs). MPS III can be caused by the deficient activity of one of four lysosomal enzymes involved in the degradation of heparan sulfate (HS), a GAG. Depending on the deficient enzyme, four subtypes (A, B, C or D) of MPS III are recognized. The continuous accumulation of HS results in progressive neurodegeneration, initially characterized by progressive cognitive impairment and behavioural problems, later followed by motor impairment and early demise. There is a wide variability in the clinical course of the disease, which is in part related to the genotype. In addition to the progressive neurological disease, a number of somatic symptoms may occur, including macrocephaly, mild coarsening of facial features, hepatomegaly, inguinal and umbilical hernias and osteonecrosis of the hip. While short stature is a prominent symptom in all other mucopolysaccharidoses (MPSs) (MPS I (OMIM #607014, 607015, 607016), II (OMIM #309900), IV (OMIM #253000, 253010), VI (OMIM #253200) and VII (OMIM #253220)), patients with MPS III have generally been reported to have normal growth. Only one publication suggests the presence of growth retardation in MPS III, based on cross-sectional data of 64 MPS III patients.

As information on growth patterns in MPS III can be important for providing optimal care, helping to avoid unnecessary investigations, and for assessment of somatic efficacy in future therapeutic studies. Therefore we studied growth patterns in a large unselected cohort of patients with MPS III, allowing assessment of differences between patients with the severe and the more attenuated phenotypes.

METHODS

Study Population

One-hundred and twenty-one patients with MPS III (70 males, 51 females) had anthropometric evaluations between the neonatal period and adulthood. Hundred-three (85%) patients were from Dutch ancestry, 7 patients (6%) were from Turkish ancestry and 6 (5%) patients were from Moroccan ancestry. Five other patients were respectively from Pakistani, Iranian (two patients), Hispanic and Austrian origin. In all patients, the diagnosis of MPS III was made by enzyme testing and/or mutational analysis. Data on height and weight were collected in a mixed retrospective and cross-sectional mode, from 1962 till 2013. If height and head circumference (HC) were assessed after 21 years of age, this was recorded as final height, HC and weight. Weight and length at birth were expressed as standard deviation scores (SDS) for gestational age. Height, weight and head circumference (HC) were expressed as SDS for age and sex for constructed MPS III specific standards.
Data were collected from medical charts from hospitals or institutions, or from the growth charts used in the Dutch child-health centers, of all Sanfilippo patients diagnosed in the Netherlands.

**Calculation of SDS**

**Patients from Dutch ancestry**

Four successive Dutch national growth studies (in 1955, 1965, 1980, and 1997) showed a clear secular trend in height and weight. However, the fifth growth study in 2010 showed no secular trend for Dutch children. Measurements in the patient population in this study were done in a period of five decades (1960–2013) and we therefore corrected the growth data obtained in the period from 1960 to 1997 for the secular trend. This was done by calculation of the SDS for the growth chart applicable for the date when height measurement was performed. We could not calculate SDS for height measurements below the 10th or above the 90th percentile for the 1955 and 1965 growth studies because SDS data for height according to age were not presented in both of these growth studies. In these cases height was corrected for secular growth between 1955/1965 and 1997 according to age. Although there is also a secular trend in weight in Dutch children, normal values for weight according to age have not been changed since the growth study of 1980. No secular trend is observed for head circumference over the last decades; therefore the data of head circumference were calculated using the 2010 growth charts.

**Patients from non-Dutch ancestry**

In 1997 and 2010 growth studies were performed for children from Turkish and Moroccan ancestry living in the Netherlands and also for them a secular trend was observed for height and weight in 2010. SDS for height of these patients were calculated for the appropriate growth chart according to date of height measurement. Because of lack of growth charts from before 1997, SDS of data on height recorded for patients from Turkish and Moroccan ancestry measured before 1997 were calculated using the 1997 growth charts. SDS of weight was calculated according to the Dutch 2010 growth charts. HC was also calculated according the Dutch 2010 growth charts, because no head circumference reference charts were available for Moroccan and Turkish patients aged over two years. For the two patients from Hispanic and Austrian ancestry, SDS were calculated using the corresponding Dutch growth charts. The three patients from Pakistani and Iranian ancestry were not analyzed in this study because of lack of appropriate growth charts.

**Assessment of phenotypic severity**

Of the 118 patients included in this growth study, 81 patients had MPS III subtype A, 22 patients subtype B and 15 patients type C (Table 1).

If feasible, patients with MPS IIIA were subdivided into three phenotypic groups based on their genotypes and according to the literature: severe, intermediate, and attenuated, and for patients with MPS IIIB into two phenotypic groups: severe and attenuated. In patients with MPS IIIC only a limited genotype-phenotype
correlation has been established, and they were therefore not included in genotype-phenotype comparisons.

**Statistical analyses**

Sex-specific centile curves for height, weight, and head circumference were constructed using the lambda, mu, and sigma (LMS) method by the Growth Analyser Research Calculation Tools software Version 4.0 (Ed. Dutch Growth Foundation, Rotterdam, Netherlands). This method is based on the principle that anthropometric data can be converted to a standard normal distribution by a Box-Cox transformation for any given age. To achieve this transformation, three smoothed age-related curves are used, namely the median curve (M curve), the coefficient of variation of the measurement as it changes with age (S curve), and the Box-Cox power needed at each age, in order to convert the data to a Gaussian distribution (L curve). A table of corresponding smoothed L, M, and S values is accessible and these values can be used to calculate any required centile or SDS curve using a simple formula that involves the L, M, and S values at any given age. The Growth Analyser software could not plot calculated SDS data (data corrected for secular trend and for other nationalities) in the same graph as the Dutch growth charts of 2010. Therefore, the calculated SDS were converted back to height as they would have been according to the Dutch growth charts of 2010, using these 2010 charts. All data were recorded in Statistical Package of Social Sciences (SPSS), version 19.0 SPSS Inc., Chicago, IL. Mean height, weight, HC, and BMI were compared with the healthy Dutch population (0 SDS) using one sample t-test. Phenotype-group comparisons for height SDS were made with a Kruskal-Wallis test for each age period of two years. However, due to few height measurements after 16 years of age the last age group consisted of a 5 year period. A *p*-value <0.05 was considered statistically significant.

**RESULTS**

**Length and weight at birth**

Information on gestational age, weight and length at birth was available for 93 MPS IIIA, 89 MPS IIIB and 24 MPS IIIC patients respectively. Since 1985, birth length in the Netherlands is infrequently measured because of a supposed increased risk for development of hip dysplasia. Therefore no Dutch reference curve is available for length at birth, and growth curves of Swedish neonates are being used in clinical practice. Ninety-one (98%) patients were born between the 37th and 42nd weeks of gestational age. Two children were born in the 36th week of gestation. Sanfilippo patients had normal birth weight (mean +/- SDS was 3504 +/- 582 gram, corresponding to 0.1 +/- 1.21 SDS); the mean birth length was 50.6 cm +/- 1.7 cm, corresponding to 0.07 +/- 1.06 SDS.

**Construction of a MPS III specific growth chart**

Of the 118 patients who were included in the study, height was recorded at 796 time points (mean: 8.3 height measurements per patient) and weight at 774 weight time points.
(mean of 10.0 weight measurements per patient). In addition, head circumference was recorded at 387 time points in these 118 patients (mean: 4.6 measurements per patient). The growth charts for male and female MPS III patients are presented Figures 1 and 2. The mean height SDS according to age was -0.48 SDS for all patients (boys -0.45 and girls -0.49 SDS). Mean height was significantly stunted in both genders (one sample t-test $p < 0.001$). The mean final height of males was 169.7 cm (+/- 9.3 cm) and females was 165.4 (+/- 9.9 cm). Compared to the normal growth charts for Dutch males and females, adult MPS III patients have a mean SDS of -2.4 and -1.0, respectively. The mean weight SDS according to age was 0.48 SDS for all patients, (boys 0.44 and girls 0.52 SDS). Mean weight was significantly elevated in both genders, $p < 0.001$. The mean adult weight of males was 60.1 +/- 9.9 kg and of females 61.1 +/- 11.6 kg, corresponding to weight SDS -1.6 and 0.22 for Dutch healthy men and women respectively. The mean BMI SDS according to age was 0.96 SDS for all patients (boys 0.89 and girls 1.0 SDS, $p < 0.001$). Forty patients (34%) were overweight (BMI > 2 SDS) at one or more time points during the study. The mean adult BMI of males was 20.4 +/- 2.2 kg/m$^2$ and females 20.2 +/- 2.7 kg/m$^2$. The mean HC SDS according to age was 0.88 SDS for all patients (boys 0.71 and girls 1.1 SDS, $p < 0.001$). The mean adult HC of males was 57.8 cm, +/- 2.1 cm and of females 57.1 cm, corresponding to HC SDS of 0.1 and 1.0 SDS for healthy Dutch men and women.

The comparison between MPS III and standard growth charts for height are depicted in Figure 3.

**INFLUENCES OF SEVERITY ON GROWTH**

In 84 of the 103 patients with MPS III type A or B, the genotype was predictive of the phenotype (Table 1). Gestational age and weight and length at birth did not differ between the three phenotypic groups. Kruskal-Wallis tests showed significant differences in the SDS for height for the different phenotypic groups in the following age groups: at ages 0-2 years ($p < 0.001$), 2-4 years ($p = 0.01$), 4-6 years ($p = 0.002$), 12-14 years ($p = 0.02$), and 16-21 years ($p = 0.001$) (Figure 4A). Growth of patients with the severe genotype seems to be accelerated during the first six years of life, while the postnatal growth of the intermediate is slightly accelerated, but only in the first two years of life. Finally, growth of the attenuated patients showed mild but constant growth impairment starting already in the first years of life. Growth is significantly impaired in patients with the severe phenotype after the age of 10 years.

**DISCUSSION**

By studying growth data in 118 unselected patients with MPS III we were able to construct disease specific standardized growth charts for this rare genetic disorder and we demonstrate a significantly stunted growth from the age of 6 years. In addition, we show that phenotypic severity, as assessed by genotyping, correlates with growth pattern and final height (Figure 4). Length and weight at birth do not differ from the control
Table 1. Clinical Characteristics.

<table>
<thead>
<tr>
<th>MPS III subtype</th>
<th>Severe</th>
<th>Intermediate</th>
<th>Attenuated</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>34 (42)</td>
<td>27 (33)</td>
<td>10 (12)</td>
<td>10 (12)</td>
<td>81 (69)</td>
</tr>
<tr>
<td>B</td>
<td>3 (14)</td>
<td>0 (0)</td>
<td>10 (45)</td>
<td>9 (41)</td>
<td>22 (19)</td>
</tr>
<tr>
<td>C</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>15 (100)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (35)</td>
<td>15 (22)</td>
<td>13 (19)</td>
<td>17 (25)</td>
<td>69 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (27)</td>
<td>12 (24)</td>
<td>7 (14)</td>
<td>17 (29)</td>
<td>49 (42)</td>
</tr>
</tbody>
</table>

* Number of cases (%).

population, which is in line with the observation that clinical signs and symptoms are rarely present in MPS III before the age of 2 years. Head circumference appears to be augmented during the first ten years of life, followed by gradual normalization, probably caused by progressive loss of brain tissue.

Our study also shows that MPS III patients in general have a higher BMI than the control population. Overweight and obesity are common in children and adolescents with intellectual disabilities. The high BMI in our MPS III cohort might be due to loss of motor function resulting in a lack of physical activity. A higher BMI might also be explained by the use of psychotropic medication (e.g. risperidon) which is frequently used for MPS III patients to control the behavioral disturbances.

Remarkably, growth in MPS III patients with the severe phenotype seems to be accelerated during the first 6 years of life. Accelerated initial growth followed by a deceleration of growth, finally resulting in short stature, has also been reported in MPS II (Hunter syndrome) in which the deceleration generally becomes evident at an age of approximately 8–10 years. Linear growth is under the control of the endocrine system and hormone-binding proteins. In addition, growth factors and their binding proteins play an additional important role. HS proteoglycans are involved in various cell signaling processes, including regulation of growth factor receptors and the accelerated growth in the first years of life might be due interference of accumulating HS or HS derived disaccharides with these delicately balanced processes. After several years, the accumulating HS and HS fragments apparently results in a shift in this balance, which might be caused by secondary mechanisms such as inflammation and induced apoptosis in the growth plates, as has been found in the MPS I and MPS II mouse models, finally resulting in growth retardation.

The predicted final height of men and women with MPS III was 169.7 cm and 165.4 cm respectively. However, the standard deviation from the predicted adult stature was 9.3 and 9.9 cm for MPS III males and females, compared to 7.1 and 6.3 cm for normal Dutch males and females respectively. This wider spectrum of final height values is most likely due to the broad spectrum of phenotypic severity.
Figure 1. Height (A and B) and weight (C and D) according to age in boys (blue, A and C) and girls (pink, B and D) with MPS III showing individual data points.
Growth in patients with mucopolysaccharidosis type III (Sanfilippo disease)

Figure 2. BMI (A and B) and head circumference (C and D) according to age in boys (blue, A and C) and girls (pink or B and D) with MPS III (with individual data points).
Growth studies have been reported for MPS I \(^{48,49}\), MPS II \(^{42,50}\), MPS IV \(^{51}\), and MPS VI \(^{52}\). Growth in MPS III is significantly less affected compared to these other MPSs. This demonstrates that HS is less deleterious on growth plates than the GAGs dermatan sulfate (DS) and keratan sulfate (KS) which accumulate in these other MPSs (in MPS I and II: DS in addition to HS, in MPS IV: KS and in MPS VI only DS).
Our study has some limitations. First, there are relatively few adult patients in the studied population as, in general, only the more attenuated patients survive into adulthood. Therefore, the final adult heights in our study may be an overestimation for the patients with a more severe phenotype if they would reach adulthood. Second, accurate measurement of height in MPS III patients can be challenging due to the behavioral problems and this may have resulted in less accurate data. Finally, the Dutch population belongs to the tallest in the world, and our disease specific standardized growth chart should therefore be used with some caution when studying MPS III patients from other ethnic backgrounds and cultural settings. However, SDS scores can be used to compare growth in MPS III patients from other regions of the world.

Growth charts are used to compare growth parameters to an applicable reference population and specific growth charts for rare genetic disorders are important to understand the natural course of growth in patients and may help management. Our study provides reliable data on growth in patients with MPS III and we demonstrate a significant effect of phenotypic severity as determined by genotype on growth. These results can be used for management of MPS III patients and can be of value for future therapeutic studies.

ACKNOWLEDGEMENTS
This study was funded by a grant from the foundation “Kinderen en Kansen”. We would like to thank S. Spaans for creating the figure with comparisons of the MPS III and Dutch reference growth curves.
CHAPTER SEVEN

REFERENCES

Growth in patients with mucopolysaccharidosis type III (Sanfilippo disease)


