Growth patterns in children with mucopolysaccharidosis I and II

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Original article

Background: **Mucopolysaccharidosis (MPS) diseases lead to a profound disruption in normal mechanisms of growth and development. This study was undertaken to determine the general growth of children with MPS I and II.**

Methods: **The anthropometric data of patients with MPS I and II (*n*=76) were retrospectively analyzed. The growth patterns of these patients were analyzed and then plotted onto Polish reference charts. Longitudinal analyses were performed to estimate age-related changes.**

Results: **At the time of birth, the body length was greater than reference charts for all MPS groups (Hurler syndrome, *P*=0.006; attenuated MPS II, *P*=0.011; severe MPS II, *P*<0.001). The mean z-score values for every MPS group showed that until the 30th month of life, the growth patterns for all patients were similar. Afterwards, these growth patterns start to differ for individual groups. The body height below the 3rd percentile was achieved around the 30th month for boys with Hurler syndrome, between the 4th and 5th year for patients with severe MPS II and between the 7th and 8th year for patients with attenuated MPS II.**

Conclusions: **The growth pattern differs between patients with MPS I and II. It reflects the clinical severity of MPS and may assist in the evaluation of clinical efficacy of available therapies.**

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Key words: **anthropometric features; longitudinal study; mucopolysaccharidosis I; mucopolysaccharidosis II**

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Introduction

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by a deficient activity of enzymes responsible for the catabolism of glycosaminoglycans (GAGs) leading to a short stature and severe joint and bone diseases.[1] Mucopolysaccharidosis I (MPS I) is caused by a deficiency of alpha-L-iduronidase (IDUA; EC 3.2.1.76) and is divided into three subtypes based on the severity of symptoms: Hurler syndrome (severe, OMIM 607016), Hurler-Scheie syndrome (intermediate, OMIM 607015), and Scheie syndrome (attenuated, OMIM 607016).[1-3] Mucopolysaccharidosis II (MPS II, Hunter disease, OMIM 309900) is an X-linked recessive disorder caused by a deficiency of iduronate-2-sulfatase (IDS, EC 3.1.6.13). Hunter syndrome affects primarily males while females are non-manifesting carriers of the condition.[1]

MPS diseases lead to a profound disruption in normal mechanisms of growth and development. Short stature is commonly observed in MPS patients and maybe secondary to a combination of structural, metabolic and endocrine abnormalities.[4] The mechanism of poor growth in the different types of MPS is not entirely understood, but may be related to the defect of the growth plate, which includes decreased matrix deposition with impaired osteoblast function, hypertrophic chondrocytes, disorganized growth plate structure and glycosaminoglycan accumulation in the growth plate.[4,5] GAG storage in MPS induces a complex sequence of such molecular abnormalities as inflammation, apoptosis (cartilage), and hyperplasia (synovial membranes), resulting in poorly organized and metabolically abnormal connective tissue matrices.[6-9] Additionally, lysosomal

GAG accumulation has been documented in the pituitary gland, thyroid gland, and testes of children with MPS II which may lead to the decreased levels of hormones critical for normal growth and development.[4]

Reports on the growth patterns of children with MPS are rare,[4,10-15] and there are no studies comparing growth patterns between different types of MPS. Currently, enzyme replacement therapy (ERT) has become available for patients with MPS I, II, and VI;[15,16] and knowledge about the natural history of MPS is necessary for a reliable evaluation of the effects of its treatment. As it is especially important to understand the dynamics of physical development, it has proven invaluable to use objective methods to assess physical development in children with MPS and in the preparation of a model of development. The purpose of this study was to determine the general growth patterns of children with MPS I and II.

Methods

Study subjects

Between 1989 and 2009, a longitudinal growth study was performed at the Children's Memorial Health Institute (CMHI), Warsaw, Poland. The protocol of this study was approved by the human-subjects institutional review board at the CMHI. A written informed consent was provided by the parents or legal guardians of the participants.Because of insufficient data for girls with MPS, the study population only consisted of boys with MPS I and II (n=76, number of measurements: 323; mean: 4.25) aged from 0.5 to 21 years (mean age for MPS I: 2.2 years; for MPS II: 7.9 years). The patients were divided into the following groups: MPS I Hurler (n=16, number of measurements: 56); the attenuated (non-neurological) form of MPS II (n=10, number of measurements: 76); and the severe (neurological) form of MPS II (n=50, number of measurements: 191). Patients with MPS I Scheie were excluded from analysis because of the lack of the data. All patients were born at term, and presented typical clinical features of MPS and had a diagnosis of MPS I or II confirmed by biochemical and molecular analyses (median age of diagnosis for Hurler syndrome: 1-2 years; for the severe form of MPS II: 3-4 years; for the attenuated form of MPS II: 5-6 years). All patients were naïve to ERT during the period of the study.

Study design

The study aimed to determine the general growth patterns in terms of height in patients with MPS I and II from birth until the introduction of ERT in comparison with the healthy population and to compare the structure of body-height growth (level, degree and direction) between patients with MPS I and II.

Anthropometric measurements

Anthropometric measurements were taken according to a standard technique and included body length/height. Until the age of 3 years, the body length of the children was measured in supine position using a liberometer (accuracy to 1 mm). The same measurements in older children were performed on standing height using a stadiometer (accuracy to 1 mm). The number of measurements of an individual patient ranged from 1 to 11, and the interval between measurements ranged from 3 months to 10 years.

Data analysis

The data for the whole group of children were divided into 24 calendar age groups. Two-tailed t test was used to compare the mean values for birth body length and weight at birth between children with MPS type I and II and the healthy children. The degree and direction of deviations of studied features in children with MPS I and II were analyzed using a data standardization method and calculated values were presented as z-scores. The growth trend for body height, weight and head circumference was assessed using the straight-line regression model.

Results

Anthropometric measurements at birth

The mean values for body height and weight at birth are presented in Table 1. The body length at birth was statistically greater in all groups than in the general

Table 1. Comparison of body length and weight at birth among boys with MPS I and II and healthy controls

Disease types	Body length (mean±SD)	Body weight (mean±SD)	Population		MPS II severe form		MPS II attenuated form	
			P value for body height	P value for body weight	P value for body height	P value for body weight	P value for body height	P value for body weight
MPS I Hurler	55.3±3.7 (n=15)	3.43±0.7 (n=15)	**0.006**	0.69	0.73	0.25	0.89	0.43
MPS II attenuated form	55.1±2.6 (n=9)	3.63±0.5 (n=10)	**0.011**	0.41	0.61	0.96		
MPS II severe form	55.6±2.6 (n=47)	3.62±0.5 (n=50)	**0.000**	0.11				
Healthy controls	52.2±2.8	3.50±0.6						

Bold font indicates statistically significant values. MPS: mucopolysaccaridosis; SD: standard deviation.

Table 2. The body height of MPS groups

Age	MPS I Hurler					MPS II severe form					MPS II attenuated form				
	Mean	*N*	SD	Min	Max	Mean	*N*	SD	Min	Max	Mean	*N*	SD	Min	Max
6 mon	70.5	2	0.71	70.0	71.0	67.5	1	-	67.5	67.5					
9 mon	75.4	7	5.16	66.5	82.5	74.0	6	3.12	68.0	76.7					
12 mon	77.2	9	6.44	68.3	87.0										
15 mon	80.8	2	8.13	75.0	86.5	81.0	1	0.00	81.0	81.0					
18 mon	83.0	2	2.12	81.5	84.5	83.1	2	0.78	82.5	83.6					
21 mon	81.1	3	8.48	72.3	89.2	87.7	3	3.21	84.0	90.0					
24 mon	89.2	3	7.82	80.3	95.0	89.0	5	2.29	85.1	90.6					
30 mon	82.9	4	4.96	77.3	87.6	96.6	4	2.20	94.5	99.2					
36 mon	87.3	2	3.89	84.5	90.0	99.1	6	4.27	95.0	105.5	98.8	2	6.79	94.0	103.6
4 y	94.1	2	4.10	91.2	97.0	104.0	12	4.91	97.8	117.0	98.0	2	-	98.0	98.0
5 y	91.5	1	0.00	91.5	91.5	108.5	15	5.40	101.0	117.5	103.7	3	3.79	101.0	108.0
6 y	96.5	2	0.71	96.0	97.0	113.9	14	5.24	106.0	123.0	112.0	1	-	112.0	112.0
7 y	97.5	1	-	97.5	97.5	113.1	13	5.40	106.5	122.0	115.5	6	5.90	105.0	122.0
8 y						114.2	12	7.10	104.0	131.0	117.67	6	8.02	108.0	126.0
9 y						117.5	11	6.83	109.0	135.0	120.0	9	7.37	108.0	129.0
10 y						117.4	14	8.12	108.0	127.5	122.1	9	8.92	110.0	133.0
11 y						118.7	7	7.38	110.7	129.6	125.6	9	8.43	112.0	136.0
12 y	103.5	1	-	103.5	103.5	118.7	5	8.68	113.0	134.0	125.2	6	9.82	114.0	138.3
13 y						119.8	4	6.46	113.0	135.4	114	1	-	114.0	114.0
14 y						121.1	3	1.41	113.0	115.0	120.3	3	10.12	114.0	132.0
15 y						121.9	3	4.79	116.7	126.1	121	2	7.07	116.0	126.0
16 y											126	2	15.56	115.0	137.0
17 y						128.7	2	14.35	118.5	138.8	116	2	0.00	116.0	116.0
18 y						119.1	1	-	119.1	119.1	123.3	4	13.18	116.0	143.0

MPS: mucopolysaccaridosis; SD: standard deviation.

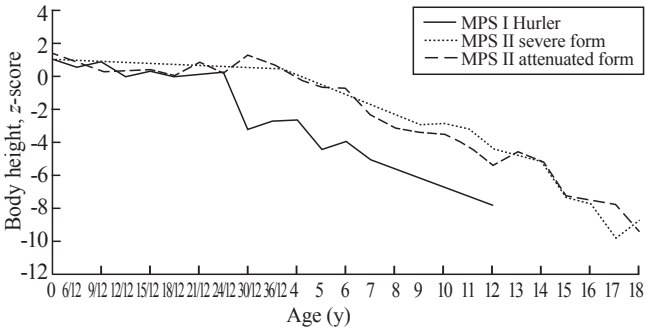

Fig. 1. The mean values of standardized body height against the adopted reference system. MPS: mucopolysaccaridosis.

population. But the differences in the birth body weight were not statistically significant (Table 1).

Tendency of growth

The basic characteristics for the body height in age classes for all groups are presented in Table 2. Individual data for this study were standardized in order to show an actual degree and the direction of deviations. Fig. 1 presents the mean standardized values for body height in calendar age groups. The results showed the existence of a characteristic downward trend in a degree and direction of deviations in MPS boys when compared with the Polish reference charts.[17] The mean *z*-score values for every MPS group showed that until the 24th month of life, the growth pattern for all MPS I and II patients was similar and the average *z*-score values for body height were greater than the reference charts (range: 0.02 to 1.71 for all groups).

Afterwards, growth patterns began to be different for individual groups. For boys with Hurler syndrome, the body height below the 3rd percentile was reached after the 24th month of life, for patients with severe MPS II between the 6th and 7th year of life, and for patients with attenuated MPS II between the 8th and 9th year. In the key moments, the differences in body height values were statistically significant only between MPS I Hurler and MPS II severe at age of 36 months (P=0.01) and 6 years (P<0.01). For other groups, the differences were not statistically significant or could not be assessed due to lack of the data. For each group after the aforementioned age, a distinct decline in the body height values was observed; the *z*-score values for body height were decreased in comparison to the reference charts. The scale of these deviations for the mean *z*-score values ranged from -0.6 to -7.8 for MPS I (Hurler syndrome), from -2.1 to -8.6 for the severe form of MPS II, and from -2.3 to -9.3 for the attenuated form of MPS II.

To show the directional changes in the growth of MPS boys, a linear-regression model was used. The above observation showed that the growth of MPS boys can be divided into two periods. Until a certain

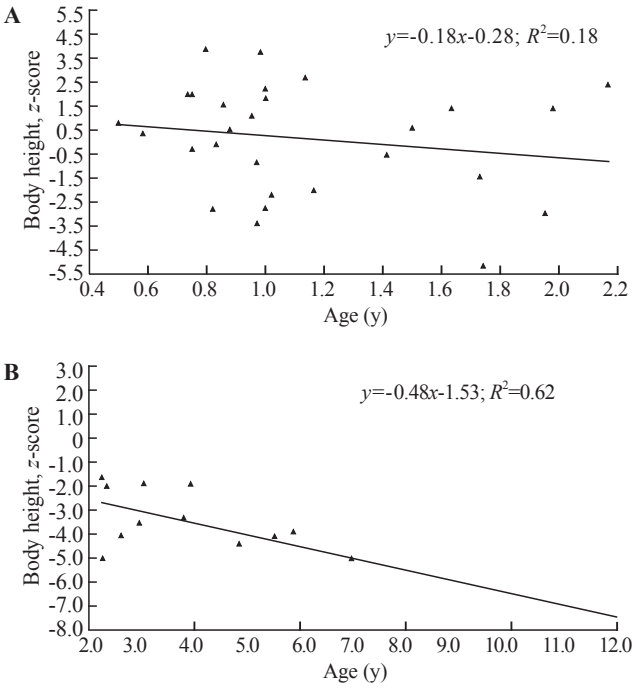

Fig. 2. The straight line regression of standardized body height for boys with MPS I Hurler until the 2nd year of life (**A**) and after the 2nd year of life (**B**) against the adopted reference system. MPS: mucopolysaccaridosis.

point in time, the pace of development was faster and the values of measurements were larger than in the general population. After this point, however, the pace of development slowed down. Additionally, the observation showed that the period of faster growth in patients with MPS II seems to be longer than in patients with MPS I. Because of this, MPS groups were divided into age groups: MPS I: until 2nd year of life and after 2nd year of life and MPS II: until 3rd year of life and after 3rd year of life. The straight-line regression model was made for each separate group to detect trends of growth at different times in ontogenesis (Figs. 2&3).

In this study, the tendency of growth for Hurler boys in both separated periods was negative. Until the 2nd year of life, this tendency was not statistically significant (P=0.34). Afterwards, negative direction became statistically significant (P=0.01). In boys with MPS II severe form, the tendency was statistically significant (P=0.04). There was an upward tendency until the 3rd year of life. Afterwards, a statistically significant negative tendency was observed (P<0.01). In boys with MPS II attenuated form, the tendency until the 3rd year of life could not be analyzed because of the lack of data. After the 3rd year, the straight-line regression model showed a statistically significant negative tendency of growth (P<0.01).

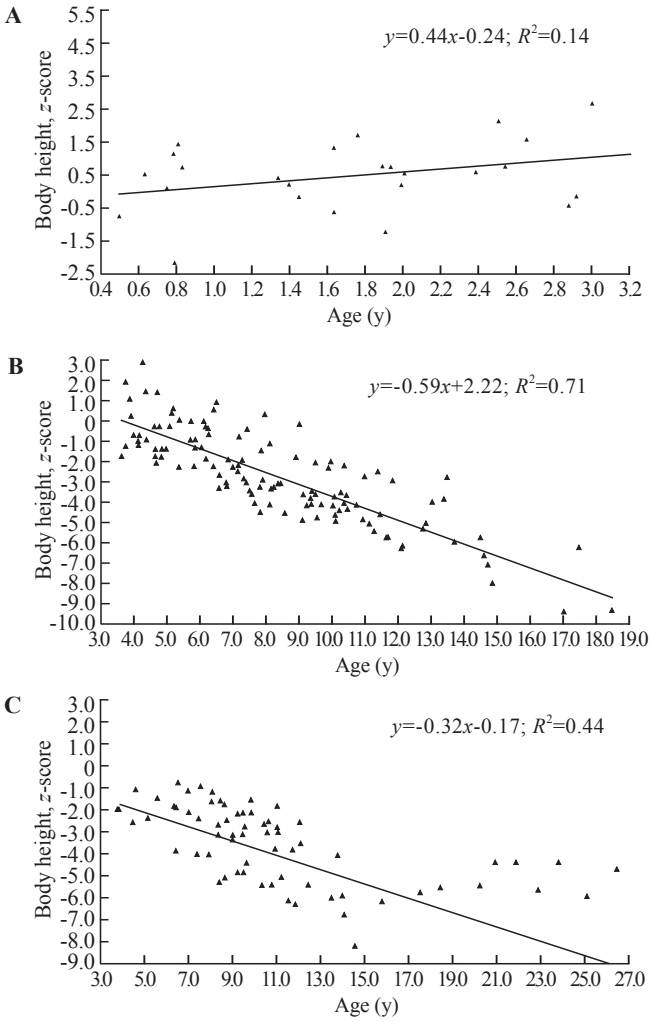

Fig. 3. The straight line regression of standardized body height for boys with MPS II severe form (**A**) and attenuated form (**B**) until the 3rd year of life and after the 3rd year of life (**C**) against the adopted reference system. MPS: mucopolysaccaridosis.

Discussion

Thorough understanding of physical development dynamics as well as all objective methods assessing the physical development of children proved invaluable in allowing us to prepare a model of development. It is important for such a model to be universal. The number of patients and the time of observation in our study indicated that it fulfilled these conditions.

The results demonstrated that the growth process of naïve boys with MPS I and II significantly differs from that of the general population. Additionally, differences between boys with MPS I and II were observed. At the time of birth, the growth process of all patients with MPS I and II was longer than that of the healthy population and the difference was statistically significant. The pathomechanism of this phenomenon is still unclear. In patients with MPS I

and II, accumulating GAGs are heparan sulfate (HS) and dermatan sulfate (DS). One hypothesis speculates that the over-growth in fetal and early postnatal life could be connected to the fact that HS, acting as a co-receptor, binds to several proteins, including growth factors. An increased level of HS might therefore over-stimulate axial bone growth in children with MPS at early developmental stages.[18] Children with MPS II, whose HS is one of the accumulated GAGs, had usually a higher or normal stature for their age.[19-21] On the other hand, the accumulation of DS over time would cause an inhibition analysis of MPS growth plates showing clusters of enlarged, GAG-containing cells that disrupt a normal columnar architecture of growth plate cartilage, presumably leading, in part, to abnormal bone growth.[7] Simonaro et al[7] suggested that the main tissue of these disorders is the cartilage rather than bone itself. Hinek and Wilson,[6] however, reported that the process of elastogenesis takes place in the shaft of long bones during fetal life and accumulations of DS lead to early disruption of normal elastogenesis. Their data suggested that dermatan sulfate-bearing moieties bind to and cause functional inactivation of the 67-KD elastin-binding protein, a molecular chaperone for tropoelastin, which normally facilities its secretion and assembly into elastic fibers.[6] In recent years, new insights into the underlying pathological mechanisms of MPS have been revealed, but further research is needed.[7-9]

Indeed, in our study the growth of patients with MPS I and II during the first 24th months of life was between 0 and 2 body height *z*-scsore (Fig. 1). Afterwards, growth slowed down after the 2nd year of life for patients with MPS I and around the 4th year of life for boys with MPS II. After this initial period of intensive growth, body height in subsequent years for patients with MPS I and II both reached significantly lower values when compared with the reference charts. Although this trend has been corroborated by earlier publications,[22,23] there is still a shortage of complementary investigations that analyze the physical development of children with MPS and carried out by appropriate specialists. The reasons for differences in growth dynamics between patients with MPS I and II during first years of life remain unknown. A greater amount of toxic DS deposited in the cartilage in patients with MPS I could explain this process. An early display of noticeable symptoms can be regarded as an indicator of the disease severity, so more severe the disease, the faster the symptoms will appear. In patients with MPS I, the disorder is detected earlier (around the 1st year of life);[24] whereas in boys with MPS II symptoms are visible later and the average age of diagnosis is 3-4 years.[25] It can be assumed that the severity of MPS is inversely proportional to survival: patients with MPS I tend to live shorter than patients with MPS II, whereas boys with the severe form of MPS II live shorter than boys with the attenuated form of MPS II.[1,25] Therefore, it can be concluded that the disease severity between MPS types (but not necessarily subtypes) can be measured by the pattern of growth.

This study has some limitations. First, the non-uniform longitudinal research[26,27] resulted in a different amount of data for calendar age groups. This situation was additionally complicated due to early mortality of patients with a severe disease form. Therefore, the greater reliability of results was obtained for the period, which was better represented. Despite these problems, this method was used in the case of rare diseases including mucopolysaccharidosis and for a robust analysis of available data. Another limitation was the difficulty of measurements in children with mental disabilities as they are restless, sometimes aggressive, and do not cooperate with a researcher. Moreover, a great number of patients had hip and knee stiffness as well as contractures of the Achilles tendon, which might have resulted in an error of measurements. Patients with a severe form of MPS died at age of 14-18 years, and even if they had lived a little longer, they could not have been measured because of their poor health condition. Finally, although we had a relatively large sample size, further studies would be desirable in order to expand our findings.

In conclusion, this study consists of a large cohort of patients with MPS with documentation of several anthropometric measurements and a comparative analysis between children with MPS I and II. Growth patterns of patients with MPS I and II differ from those of the general population as well as between MPS I and II. Since patients with MPS tend to be larger than the healthy population, two phases of ontogeny can be disclosed: the first is different for patients with MPS I and MPS II, and the second is similar for both groups and clearly shows a trend of pathological deviations in comparison with healthy peers. The growth patterns in this study present a reference model of growth.

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Ethical approval: The protocol of this study was approved by the Human-Subjects Institutional Review Board at the Children's Memorial Health Institute. A written informed consent was provided by the parents or legal guardians of the participants.

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Contributors: RSA: anthropometric measurements, interpretation of data, drafting and revising the article; JA: conception and design, conduct of the work, drafting and revising the article; CJ: conception and design, interpretation of data, revising the article; TSA: conception and design, conduct of the work, drafting and revising the article.

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