Can Macrosomia or Large for Gestational Age Be Predictive of Mucopolysaccharidosis Type I, II and VI?

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Key Words
anthropometric features; large for gestational age; macrosomia; mucopolysaccharidosis; overgrowth

Background: The objective of the study was to compare mean values for birth body length and weight between patients with mucopolysaccharidosis (MPS) and the general population.

Methods: A retrospective analysis of birth anthropometric data was performed for patients (n = 103) with MPS I, II, and VI. Two-tailed t tests were used to compare mean values for body length and weight at birth between patients with MPS and the general population.

Results: Mean values for birth body length and weight for all studied groups were greater than in the general population. For body length the differences were statistically significant. When considered individually, 53% of patients were large for gestational age (LGA) and 30% were macrosomic. The highest percentage of LGA was observed in MPS II males and MPS VI females (55% and 56%, respectively), while the highest percentage of macrosomia was observed in MPS VI males (36%).

Conclusion: At the time of birth, MPS patients were larger than those in the general population. High birth weight and/or LGA can be suggestive of MPS disease and should raise suspicion aiding early disease recognition.

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1. Introduction

Mucopolysaccharidoses (MPSs) 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 disease.1-4 Mucopolysaccharidosis type I (MPS I) is caused by a deficient activity 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 600701), Hurler--Scheie syndrome (intermediate, OMIM 601705), and Scheie syndrome (attenuated, OMIM 601706).1-3 Mucopolysaccharidosis type II (MPS II, Hunter disease, OMIM 309900) is an X-linked recessive disorder caused by a deficient activity of iduronate-2-sulfatase (IDS, EC 3.1.6.13). Hunter syndrome affects primarily males while females are nonmanifesting carriers of Condition 1. Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome, MPS VI, OMIM 253200) is caused by a deficient activity of N-acetylgalactosamine-4-sulfatase (4-sulfatase, arylsulfatase B, ARSB, EC 3.1.6.12).1-4

Human growth is a multi-factorial and complex process, involving physiological interplay between nutritional, endocrine, and metabolic factors, on a wider background of variation in genetic traits and environmental exposure.5 MPS diseases lead to a profound disruption in normal mechanisms of growth and development.6 The underlying cause of degenerative bone and joint disease is a lack of skeletal remodeling, disordered endochondral and intramembranous ossification, disruption of normal elongation, and the infiltration by GAGs of the ligaments, tendons, joint capsules, and other tissue structures.7-9 GAG storage in MPS induces a complex sequence of molecular abnormalities leading to inflammation, apoptosis (cartilage), and hyperplasia (synovial membranes), resulting in poorly organized and metabolically abnormal connective tissue matrices.7-9

In our previous studies, we evaluated and compared growth patterns in patients with MPS I (n = 14) and MPS II (n = 28).12-14 In this study, which deals exclusively with birth parameters, additional data as well as MPS VI patients were added to compare birth body length and weight between MPS I, II, VI, and the general population.

2. Methods

2.1. Study participants

A retrospective analysis (years 1989–2012) of birth anthropometric data (n = 103) was performed for patients with MPS I (18 boys), MPS II (56 boys), and MPS VI (11 boys and 18 girls). All patients with MPS I and II were of Polish origin, while patients with MPS VI were of Polish (n = 11), Russian (n = 8), Lithuanian (n = 6), Belarusian (n = 2), and Estonian (n = 2) origin. Birth data were collected from health books of each patient. All measurements were performed at the time of birth, in hospitals where the children were born.

All patients were born at term (prematurely born patients were excluded from the study), and presented typical clinical features of MPS and had a diagnosis of MPS type I, II, or VI confirmed by biochemical and molecular analyses.

All patients were naive to enzyme replacement therapy (ERT) during the time of the study.

2.2. Study design

The study objectives were to compare mean values for birth body length and weight between patients with MPS I, II, VI, and the general population.5

2.3. Anthropometric measurements

Anthropometric measurements were taken according to a standard technique and included body length/height. Length was measured in the supine position using a tape measure. The body weight was measured using an electronic scale accurate to within 0.05 kg.

2.4. Data analysis

Two-tailed t tests were used to compare mean values for body length and weight at birth between patients with MPS I, II, VI, and the general population.

2.5. Ethical consideration

The protocol was approved by the Human-subjects Institutional Review Board at the Children’s Memorial Health Institute, Warsaw, Poland. A written informed consent had to be provided by parents or legal guardians.

3. Results

Mean values for birth body length and weight for all studied groups were greater than in the general population (Table 1). For body length the differences were statistically significant (Figure 1). LGA was defined as a weight, length, or head circumference that lies above the 90th percentile for gestational age. Macrosomia, which literally means "big body," is defined by the American College of Obstetricians and Gynecologists, as birth-weight > 4000 g or > 4500 g irrespective of gestational age. When considered individually, 53% of patients were large for gestational age (LGA) and 30% were macrosomic. The highest percentage of LGA was observed in MPS II males and MPS VI females (55% and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean value of body weight and length in the studied population.</th>
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<tbody>
<tr>
<td>No.</td>
<td>Group (n)</td>
</tr>
<tr>
<td>1</td>
<td>MPS I (18)</td>
</tr>
<tr>
<td>2</td>
<td>MPS II (56)</td>
</tr>
<tr>
<td>3</td>
<td>MPS VI</td>
</tr>
<tr>
<td>Boys (11)</td>
<td>55 ± 3.59</td>
</tr>
<tr>
<td>Girls (18)</td>
<td>53.8 ± 2.89</td>
</tr>
<tr>
<td>4</td>
<td>Healthy population</td>
</tr>
<tr>
<td>Boys</td>
<td>52.2 ± 2.8</td>
</tr>
<tr>
<td>Girls</td>
<td>51.3 ± 2.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. MPS = mucopolysaccharidosis.
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Figure 1  Mean value of birth length comparison with general population. * Statistically significant, p < 0.01. † Statistically significant, p = 0.04. ‡ Statistically significant, p = 0.01. MPS = mucopolysaccharidosis.

56%, respectively, while the highest percentage of macrosomia was observed in MPS VI males (36%). There was no clear correlation between birth parameters and type of MPS or severity of the disease.

4. Discussion

In our previous studies, we evaluated and compared growth patterns in patients with MPS I (n = 14) and MPS II (n = 28).12–14 In this study, which deals exclusively with birth parameters, additional data as well as MPS VI patients were added in order to compare birth body length and weight between MPS I, II, VI, and the general population. In our cohort, mean values for birth body length and weight were greater than the general population with values for birth body length being statistically significant. When considered individually, 53% of patients were LGA and 30% were macrosomic. There is a scarcity of literature about birth measurements of patients with mucopolysaccharidoses. In a Brazilian study, the mean birth weight for MPS II patients with an attenuated or severe form of the disease was not significantly higher compared with that for Brazilian male newborns.16 However, around 25% of all Brazilian patients weighed more than the 90th percentile (3.75 kg) at birth and 7.8% weighed more than 4.3 kg, which is similar to our results.16 Unfortunately, no length measurements were provided in this study. The major limitation of our study is associated with methods used to measure children’s length at birth. As it is very difficult to measure newborns, birth measurements may include observational errors. Although the measuring methods are universal and the same methods were also used to construct reference charts, they can still include minor errors when compared with real length.

Macrosomia is associated with numerous perinatal and maternal complications.17 Increased numbers of high birth weight infants and LGA have been reported in North America and Europe.18–20 Increases in maternal anthropometry, reduced cigarette smoking, and changes in sociodemographic factors have been suggested to lead to an increase in the weight of infants born at or after term.19 LGA is an indication of high prenatal growth rate and is associated with several risk factors. One of the primary risk factors is poorly controlled diabetes, particularly gestational diabetes mellitus (GDM), as well as preexisting type 2 diabetes mellitus (DM; Table 2). The risk of macrosomia is directly related to maternal hyperglycemia (twice as high as in the control group with glucose levels exceeding 130 mg/dL).21 Apart from maternal hyperglycemia and fetal hyperinsulinemia, insulin-like growth factors and selected adipocytokines produced by adipose tissue and placenta are among the factors contributing to the development of diabetic fetopathy.21 Maternal obesity, weight gain during pregnancy and maternal hyperlipidemia seem to be other factors involved in the pathogenesis of feto-maternal complications. It is important to keep in mind that taller, heavier parents also tend to have larger babies (familial tall stature). The differential diagnosis within LGA includes a group of rare genetic causes such as overgrowth syndromes, which have significant clinical and molecular overlap and are associated with developmental delay, tumors, and other anomalies (Table 2). Congenital overgrowth is defined by a neonatal weight above the 97th percentile.22 The main differential diagnoses are Sotos syndrome (OMIM 117350), Weaver syndrome (WVS, OMIM 277590), Beckwith-Wiedemann syndrome (BWS, OMIM 130650) and Simpson dysmorphism syndrome (SDYS, Simpson-Golabi-Behmel syndrome, SGBS1, OMIM 312870).23–26 Sotos syndrome is an autosomal dominant overgrowth syndrome with four major diagnostic criteria: overgrowth with advanced bone age, macrocephaly, characteristic facial appearance, and developmental delay.25 It shows considerable phenotypic overlap with Weaver syndrome (Table 2). Beckwith-Wiedemann syndrome (BWS) is a pediatric overgrowth disorder with an increased risk of developing embryonic tumor development, such as Wilms’ tumor and hepatoblastoma. The clinical presentation is highly variable; some cases lack the hallmark features of exomphalos (umbilical hernia, abdominal wall defects), macroglossia, and neonatal gigantism as originally described by Beckwith26 and Wiedemann et al.27 SGBS is an X-linked condition characterized, similarly to BWS, by overgrowth, visceromegaly, and numerous morphological abnormalities.28 It was initially described as a condition resulting in a bulldog-like appearance.29 In addition, patients are at high risk for Wilms’ tumor and neuroblastoma.29 The above description of the various overgrowth syndromes shows that there is no developmental anomaly unique to a specific syndrome and that the syndromes may involve overlapping signaling pathways.30 As there exists a wide spectrum of syndromes, disorders resulting in overgrowth can represent a diagnostic and therapeutic challenge.25

The majority of MPS children are born after uncomplicated pregnancies with normal birth and family history, with initial signs and symptoms emerging between the ages of 18 months and 4 years, depending on disease severity.31 The most common presenting feature is a coarsening of facial features, which becomes apparent between 2 years and 4 years of age (Table 2, Figure 2).32 Early developmental milestones may also be normal, even in the presence of significant somatic disease. The neonatal period in attenuated forms may be normal, while in severe types of the disease some symptoms might occur early after birth such as inguinal or umbilical hernias and in the case of MPS II there is an increased incidence of Mongolian blue spots.35
Table 2  Differential diagnosis between mucopolysaccharidosis types I, II, and VI and other disorders presenting with high birth weight and/or large for gestational age.

<table>
<thead>
<tr>
<th>Disease (abbreviation, OMIM No.)</th>
<th>Manifestations</th>
<th>Inheritance/genetic alterations</th>
<th>Diagnosis</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I (OMIM 607016, OMIM 607015, OMIM 607016)</td>
<td>- Facial features (thickening of the alae nasi, lips, ear lobules, &amp; tongue), plethoric, rosy-cheeked appearance</td>
<td>- Autosomal recessive (MPS I, MPS VI)</td>
<td>- Urine GAG levels</td>
<td>1,13,14</td>
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<tr>
<td>MPS II (OMIM 309900)</td>
<td>- Facial &amp; body hypertrichosis (scalp hair—coarse, straight, &amp; thatch-like hair)</td>
<td>- X-linked recessive (MPS II)</td>
<td>- Enzyme assay</td>
<td>4</td>
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<tr>
<td>MPS VI (OMIM 253200)</td>
<td>- Umbilical/inguinal hernia</td>
<td></td>
<td>- Mutation analysis</td>
<td>1,13,14</td>
</tr>
<tr>
<td>Cerebral gigantism (Sotos syndrome, SS, 117550)</td>
<td>- Rapid overgrowth with advanced bone age</td>
<td>- Sporadic in 95% of cases</td>
<td>- 4 major diagnostic criteria (overgrowth with advanced bone age, macrocephaly, characteristic facial appearance, &amp; learning difficulties)</td>
<td>5,23–26</td>
</tr>
<tr>
<td></td>
<td>- Macrocephaly</td>
<td>- The majority of patients show a partial deletion or mutation of the NSD1 gene encoding nuclear receptor SET-domain-containing protein 1 on chromosome 5q35</td>
<td>- Molecular diagnosis is important (NSD1 mutations &amp; deletions)</td>
<td>5,23–26</td>
</tr>
<tr>
<td></td>
<td>- Characteristic facial appearance (high bossed forehead, sparse frontotemporal hair, malar flushing, long narrow face, downsloping palpebral fissures, prominent narrow jaw)</td>
<td></td>
<td>- The molecular basis of WS is unknown</td>
<td>23,25,26</td>
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<td></td>
<td>- Learning disability (delay of early developmental milestones, hypotonia, poor coordination, language delay, intellectual impairment) developmental delay</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- Pre- &amp; post-natal overgrowth</td>
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<td></td>
<td>- Advanced osseous (carpal) maturation</td>
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<td></td>
<td>- Characteristic craniofacial features (microgenathia with a deep horizontal chin crease)</td>
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<tr>
<td></td>
<td>- Developmental delay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weaver syndrome (WS, WVS, Marshall-Smith syndrome, 277590)</td>
<td></td>
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<tr>
<td>Beckwith–Wiedemann syndrome (BWS, 130650)</td>
<td>- Increased growth rate during the latter half of pregnancy &amp; in the 1st few years of life (neonatal gigantism)</td>
<td>- Variable; sporadic in 85% of cases, but can be autosomal dominant; also can be caused by uniparental disomy &amp; imprinting defects</td>
<td>Diagnosis is based on clinical findings, a ‘mild’ presentation may include prominent tongue &amp; umbilical hernia</td>
<td>5,23–26,32</td>
</tr>
<tr>
<td></td>
<td>- Macroglossia</td>
<td>- The mode of inheritance of BWS is complex. The current understanding of the molecular basis of the syndrome is that aberrations in the chromosomal region 11p15.5 involving imprinted genes have a pivotal</td>
<td></td>
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<tr>
<td></td>
<td>- Increased frequency of malformations (abdominal wall defects: omphalocele, umbilical hernia, diastasis recti; renal anomalies: renal medullary dysplasia, nephrocalcinosis, nephrolithiasis)</td>
<td>- Autosomal dominant inheritance has been reported</td>
<td></td>
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<tr>
<td></td>
<td>- Visceromegaly (liver, spleen, pancreas, kidneys, adrenals)</td>
<td>- NSD1 mutation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- Predisposition to embryonal malignancies (Wilms tumor &amp; hepatoblastoma)</td>
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1. A. Rożdżyńska-Świątkowska et al.
The age of diagnosis is usually between 9 months and 36 months, but may be significantly delayed in attenuated forms. Including MPS disease in the diagnostic algorithm of LGA and macrosomia may increase the chances of diagnosing these patients very early in life, which is crucial for efficient treatment.

The pathomechanism of the prenatal and early postnatal overgrowth in MPS disease remains unclear. Linear growth during childhood occurs primarily from chondrocyte differentiation and replication at the growth plate in the distal epiphyseal and central metaphyseal regions of long bones. Childhood growth is stimulated by human growth hormone (hGH), which is secreted in a pulsatile manner from the anterior pituitary, primarily under the control of hypothalamic growth hormone releasing hormone (e.g., ear anomalies, neonatal hypoglycemia, nephromegaly, & hemihyperplasia) is required for the postnatal clinical diagnosis of BWS. A careful cytogenetic analysis of the 11p15 region is recommended. Prenatal diagnosis by ultrasonography is possible. Molecular diagnosis is important to confirm the provisional BWS clinical diagnosis & to identify BWS patients with cancer susceptibility. Diagnosis is based on clinical findings, a family history consis-tence with X-linked inheri-tance, & the results of molecular genetic testing of GPC3. The molecular basis of Perlman is unknown.

Table 2 (continued)

<table>
<thead>
<tr>
<th>Disease (abbreviation, OMIM No.)</th>
<th>Manifestations</th>
<th>Inheritance/genetic alterations</th>
<th>Diagnosis</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson-Golabi-Behmel syndrome, Simpson dysmorphia syndrome (SGBS, SDYS, 312870)</td>
<td>- Pre- &amp; postnatal overgrowth - Coarse facies - Congenital heart defects - Other congenital abnormalities (dysplastic kidneys, vertebral &amp; rib defects, postaxial hexadactyly, supernumerary nipples) - High risk for Wilms tumor &amp; neuroblastoma</td>
<td>- X-linked recessive - Defects involving the GPC3 (glypican 3) gene, located on Xq26, which encodes an extracellular proteoglycan believed to function in growth regulation</td>
<td>(e.g., ear anomalies, neonatal hypoglycemia, nephromegaly, &amp; hemihyperplasia) is required for the postnatal clinical diagnosis of BWS. A careful cytogenetic analysis of the 11p15 region is recommended</td>
<td>5,23–26</td>
</tr>
<tr>
<td>Perlman syndrome</td>
<td>- Fetal overgrowth &amp; neonatal macrosomia - Polyhydramnios - Visceromegaly - Nephromegaly - Predisposition (bilateral) for Wilms’ tumor - Macrocephaly, dysmorphic facial features (micrognathia, round face, broad flat nasal bridge) - Mental retardation</td>
<td>- Autosomal recessive</td>
<td></td>
<td>5,23–26</td>
</tr>
</tbody>
</table>

BWS = Beckwith–Wiedemann Syndrome; GAG = glycosaminoglycan; GPC3 = glypican 3; MPS = mucopolysaccharidosis; NSD1 = nuclear receptor SET-domain-containing protein 1; OMIM = Online Mendelian Inheritance in Man; WS = Weaver syndrome.
hormones also exert growth promoting effects at the growth plate. In MPS I, II, and VI accumulating GAGs are heparan sulfate (HS, in MPS I and II) and dermatan sulfate (DS, in MPS I, II, and VI). HS is one of the most prevalent types of GAGs found on the cell surface and is not a unique structure but a collection of related molecules with different patterns of sulfation as well as other modifications. These structural variants are found in tissue-specific distributions and show age- and disease-related changes. HS is a negatively charged molecule that binds to a variety of extracellular proteins, including growth factors and HS-modified proteoglycans (HSPGs) serving as growth-factor coreceptors, which affect the delivery or assembly of ligands into signaling complexes. Bishop et al speculate that the over-growth in fetal and early postnatal life could be connected to the fact that HS, acting as a coreceptor, binds to several proteins, including growth factors. An increased level of HS might therefore overstimulate axial bone growth in children with MPS at early developmental stages. Hinek and Wilson showed that the process of elastogenesis took 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-kDa elastin-binding protein, a molecular chaperone for tropoelastin, which normally facilitates its secretion and assembly into elastic fibers. Additionally, lysosomal GAG accumulation has been documented in the pituitary and thyroid gland of MPS II children.

5. Conclusion

At the time of birth, many MPS patients are larger than the general population. High birth weight and/or LGA can be suggestive of MPS disease and should raise suspicion aiding in early disease recognition.

Conflicts of interest

A.J. is currently a full-time employee of Shire Pharmaceuticals, however she did not have any conflict of interest at the time of the study or at the time of preparation of the manuscript. The other authors declare no conflicts of interest.

Acknowledgments

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