Chapter 126
Impairment of Body Growth in Mucopolysaccharidoses

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Abstract

Children with mucopolysaccharidoses (MPS) grow poorly and become physically handicapped because of systemic bone disease. For children with skeletal dysplasias, such as MPS, it is important to know the natural history of growth. Understanding of the growth pattern provides assessment of current growth and data on efficacy of individualized medicine in growth-promoting treatments. The purpose of this chapter is to review natural history of growth patterns for MPS II, IVA, and VI patients. The cross-sectional and/or longitudinal data were collected to develop growth curves for the following types of MPS. Interestingly, accelerated growth has been observed in the first years of life in any type of MPS reviewed here, followed by slowing growth rate and growth failure. (1) MPS II: We obtained height and weight measurements from 46 Japanese male patients with MPS II. Mean birth length of boys was 50.9 ± 2.1 cm. The mean height for MPS II at 18 years of age or older was 127.2 ± 8.5 cm. These values corresponded to 0.9 SD and −7.5 SD of the height for normal Japanese males. The mean height was kept higher until 5 years and the mean weight was heavier until 8 years of age. After 7 years of age, short stature was commonly observed in spite of clinical severity by CNS involvement. (2) MPS IVA: Height and weight measurements from 193 girls and 195 boys with MPS IVA were collected. Mean birth lengths of boys and girls were 52.4 ± 3.9 and 52.1 ± 2.9 cm, respectively. Mean heights for males and females at 18 years of age were 119.3 ± 22.6 and 113.5 ± 23.1 cm, respectively. These values correspond to −8.0 SD and −7.7 SD of the mean height for normal males and females. Mean birth weights for boys and girls were 3.56 ± 0.5 and 3.5 ± 0.7 kg, respectively. (3) MPS VI: Growth is severely impacted on this type of MPS. In an observational study in 121 untreated MPS VI patients, a mean height was 115.2 cm ± 26.1 cm and median height was 103.7 cm with a range of 80–169 cm. An inverted correlation of height with the excretion of urinary GAGs and an influence of the genotype on the pattern of this excretion were also demonstrated. Thus, the growth pattern in MPS II patients was characterized by impaired growth velocity after 4 years of age, while the growth patterns in MPS IVA and VI patients were characterized by impaired growth velocity after 1 and 2 years of age.

Abbreviations

BMI Body mass index
CDC Centers for Disease Control and Prevention
CS Chondroitin sulfate

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126.1 Introduction

The mucopolysaccharidoses (MPS) are a group of diseases characterized by various deficiencies of enzymes required for degradation of complex carbohydrates. The enzymatic deficiencies result in the lysosomal accumulation of chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), and/or keratan sulfate (KS) in various tissues resulting in multi-system complications (Neufeld and Muenzer, 2001). Therapies for MPS have been developed clinically and experimentally. These include hematopoietic cell transplantation (HCT), enzyme replacement therapy (ERT), and gene therapy, all of which lead to the partial restoration of the enzyme activity. HCT and ERT have significantly improved the duration and quality of life for these children affected by MPS. Treating LSDs with ERT relies on the cellular uptake of enzyme by receptor-mediated endocytosis. ERT was approved for use in patients with mucopolysaccharidosis I (MPS I) (Kakkis et al., 2001), MPS II (Muenzer et al., 2002, 2006), and MPS VI (Harmatz et al., 2004, 2005, 2006). Patients treated with HCT and ERT had clinical improvement of somatic manifestations and improved quality of life. Thus, both HCT and ERT are a promising therapy for liver, spleen, respiratory, and cardiovascular complications of these diseases. However, there is a limited effect by ERT on neurological, musculoskeletal, growth, and endocrine abnormalities, although the long-term benefit of these treatments is largely unknown.

A child’s growth is one of the best indicators of overall health and it can be impacted by poor nutrition, insufficient growth or thyroid hormones, abnormal bone metabolism, chronic disease, and social isolation. Short stature is commonly observed in MPS patients and is likely secondary to a combination of structural, metabolic, and endocrine abnormalities. The characteristic skeletal abnormalities of MPS, especially in MPS IVA (kyphoscoliosis and genu valgum), limit growth and final height. However, this does not entirely account for the short stature since it is found in MPS patients even without severe abnormal spine curvatures or genu valgum. The mechanism of poor growth in the different types of MPS is not entirely understood but may be related to defect of the growth plate which includes decreased matrix deposition with impaired osteoblast function, hypertrophic chondrocytes, disorganized growth plate structure, and glycosaminoglycan (GAG) accumulation in the growth plate (Russell et al., 1998; Abreu et al., 1995; Silveri et al., 1991; Nuttall et al., 1999; Monroy et al., 2002). Lysosomal GAG accumulation has been also documented in the pituitary gland, thyroid gland, and testes of children with MPS II (Oda et al., 1988; Nagashima et al., 1976), and in ovarian tissue of a murine model of MPS VII (Soper et al., 1999). Growth hormone, thyroid hormone, and sex hormones are all critical for normal growth and development. Low insulin-like growth factor-1 (IGF-1) levels have been reported in MPS II (Toledo et al., 1991). Hypothyroidism, growth hormone
(GH) deficiency, low IGF-1, and precocious puberty were found in children with a severe form of MPS I after HCT (Polgreen et al., 2008).

For children with skeletal dysplasias, or other syndromes affecting height, it is important to know the natural history of growth. As in otherwise healthy children, these expected growth patterns provide a measure of health and assessment of efficacy of treatment. Expected growth can also help families make individualized decisions about growth-promoting treatment options. Short stature in MPS can be quite severe, frequently $-3$ to $-9$ SD below the mean height for age and gender. Short stature limits activities of daily living and can negatively impact social development, socio-economic status, and career advancement (Zimet et al., 1997; Ross et al., 2004; Gollust et al., 2003).

Growth is a fundamental and integral marker in children with MPS. Children with MPS are known to grow poorly compared to age-matched healthy children, but it is unclear whether this poor growth is “normal” for the MPS population or a marker of some secondary condition that requires further evaluation and treatment. In pediatric practice, “poor” growth is equated with poor health. Infant growth is a determinant of adult bone mass, and poor childhood growth is a risk for bone fracture (Oliver et al., 2007). Poor growth is determined by careful measurement and comparison of the results to appropriate reference standards. Since growth and final height differ markedly between MPS and healthy children, standard growth charts should not be used for children affected with a group of these disorders to assess the severity or prognosis of the disease or the efficacy of treatment. These standard curves developed for the general population cannot be used to assess the growth of an individual affected by MPS. Several syndrome-specific charts have been described previously (Myrelid et al., 2002; Witt et al., 1986; Butler and Meany, 1987; Gawlik et al., 2006; Martin et al., 2007); however, appropriate growth curves for these children with MPS have not been established until recently (Montaño et al., 2008). For this reason, efforts have been made to develop growth curves specific for each type of MPS.

This chapter describes the published and unpublished data on growth in children with MPS, especially MPS I, II, and VI, and reviews the correlation between growth and markers of health and physical activity if available. Two limitations of studies are the following: (1) each MPS disease is quite rare, leading to limited number of data from each individual population, and (2) collected data contain patients from diverse ethnic backgrounds except Japanese MPS II described here. One argument is how we can compare our current data with a normal control population. One would like to compare the growth charts on the same ethnic background like Japanese MPS II patients. It would also be ideal to have growth charts considering different socioeconomic background for each population. However, current growth charts do not exist to cover all of the relevant populations. Recent studies made a compromise by comparing the growth charts from a certain small population with those from non-specific normal populations like growth charts from the Centers for Disease Control and Prevention (CDC) (Ayatollahi and Pourahmad, 2006; Clementi et al., 1999; Erkula et al., 2002; Hauffa et al., 2000; Marinescu et al., 2000). Therefore, we have selected CDC growth charts which include updated reliable data containing diverse ethnic backgrounds (Ogden et al., 2002; Kuczmarkska et al., 2002) to compare with MPS IVA patients. We expect that in the future the databases will be improved by including higher variation of normal population for better comparison purposes.

126.2 Mucopolysaccharidosis II (Hunter Syndrome) (OMIM 309900)

MPS II is an X-linked recessive trait characterized by systemic anomalies including short stature, joint contracture, dysmorphic facial appearance, dysostosis multiplex, respiratory dysfunction, airway obstruction, hearing and visual disturbances, heart valve disorders, and hepatosplenomegaly. Patients with the severe phenotype of MPS II manifest psychomotor retardation and neurological
regression. MPS II is caused by deficiency of iduronate-2-sulfatase. This enzyme hydrolyzes the sulfate moiety of GAGs, DS, and HS. Incidence of MPS II is 0.6–1.3 per 100,000 male live births (Martin et al., 2008). MPS II is the most common subtype of MPS in Japan, comprising more than 50% of MPS patients.

126.2.1 Clinical Aspects

MPS II is a disease with multiorgan and multisystem involvement that has a variable age of onset and a variable rate of progression. The clinical manifestations include mental retardation, motor and language developmental delay, behavioral disturbances, short stature, sleep apnea, seizures, umbilical and inguinal hernias, carpal tunnel syndrome, restrictive range of motion, hepatosplenomegaly, and coarse facies. The traditional classification of patients into “mild” or “severe” subtypes, on the basis of the length of survival and the presence or the absence of CNS disease, is a gross simplification. The disorder should rather be regarded as a continuum between two extremes (attenuated and severe). It is important to note that individuals with an attenuated form of the disease may still have symptoms and complications that lead to significant morbidity and disability, and may present with mild-to-moderate learning difficulties. Although the clinical course for the more severely affected patients is relatively predictable, there is considerable variability in the clinical phenotype and progression of the more attenuated form of the disease. Individuals with attenuated MPS II are most often diagnosed between the ages of 4 and 8 years. An extremely attenuated case was diagnosed at 29 years of age (Suzuki et al., 2009). In its severe form, clinical features appear between 2 and 4 years of age. In these cases, progressive neurological involvement is prominent and progresses to severe mental impairment. Death usually occurs in the first or second decade of life, usually because of obstructive airway disease and/or cardiac failure associated with loss of neurological function. At the opposite end of the spectrum, clinical signs and symptoms have a slightly later onset, but neurological dysfunction is minimal. These patients have normal intelligence and survive into adulthood.

126.2.2 Skeletal Abnormalities

The skeletal abnormalities are similar regardless of the severity of the phenotype. Patients typically appear normal at birth. The patients tend to have broad noses with flared nostrils, prominent supraorbital ridges, and large jowls. The head is of large circumference throughout life. Mobility is restricted because of joint stiffness and contractures (Fig. 126.1). The skeletal findings of MPS II, along with other MPS diseases, are collectively known as dysostosis multiplex. Radiographic examination reveals abnormal thickness of all bones and irregular epiphyseal ossification in the joints of the hand, shoulder, and elbow. The hands are reported to take on a claw-like appearance, and, in combination with carpal tunnel syndrome, loss of hand function will appear. The ribs are thickened and have an unusual shape, and clavicles can be increased in bulk. The lateral surfaces of the vertebral bodies are irregularly notched in appearance (Schwartz et al., 2007). These skeletal changes result in profound loss of joint range of motion and restricted mobility. Patients with MPS II often walk on their toes because of joint stiffness and tight heel cords.

126.2.3 Growth

Patients with MPS II appear normal at birth, although they tend to be heavier and taller (see below in Section 126.2.3.2). Affected children are described to keep normal growth during early infantile
period and the growth is impaired after age 5; however, the growth chart of MPS II is not available so far. We reviewed the growth pattern in two MPS II populations (Brazilian and Japanese).

126.2.3.1 Brazilian MPS II

All patients, including a female patient, presented with the typical clinical features of MPS II. The clinical data were obtained from 77 Brazilian patients. The charts for weight, head circumference, and height at the last evaluation for patients under 18 years were investigated.

Length and Height

The mean birth length for Brazilian MPS II patients was 50.0 ± 2.1 cm, indicating that there is no difference compared with the Brazilian healthy newborns. Records of height showed that the height of most patients was above −2 SD of the Brazilian mean until approximately 7.8 years of age. After this age, the height for the majority of patients was between −2 and −6 SD of the mean (Schwartz et al., 2007). Short stature was commonly observed in spite of attenuated or severe phenotype (over 90% were below −2 SD of the mean height for age-matched control population).
Weight

The mean birth weight for Brazilian MPS II patients was $3.36 \pm 0.6$ kg. The mean birth weight found for the patients with the attenuated or severe form of the disease was not significantly higher compared with that for Brazilian male newborns. However, around 25% of all patients weighed more than the 90th percentile (3.75 kg) at birth and 7.8% weighed more than 4.3 kg. Weight records indicated that some children weighed above 2 SD of the mean for age-matched controls until 5 years of age. Between 5 and 10 years of age, the weight for most children remained between ± 2 SD of the mean for age-matched controls. After 10 years of age, values recorded for most children were below 2 SD of the mean for age-matched controls. Measurement of head circumference revealed that macrocephaly was common at all ages.

126.2.3.2 Japanese MPS II

No standard growth chart in MPS II has been known for any population. We have established the growth chart for Japanese MPS II based upon 325 and 319 measurements (height and weight, respectively) from 46 male patients with MPS II. The charts for weight and height at multi-measurements for patients were investigated.

Length and Height

The mean birth length for affected boys was $50.9 \pm 2.1$ cm ($n = 39$) which corresponded to +0.9 SD for boys ($49.0 \pm 2.1$ cm) on the Japanese standard growth charts (Fig. 126.2). Records of height showed that the mean height for the patients was higher than that for age-matched controls until

![Fig. 126.2 Birth length of MPS II patients with attenuated or severe form (copyright belongs to Gifu and Saint Louis Universities)](image-url)
approximately 6.0 years of age (Fig. 126.3). However, between 6 and 7 years of age, the mean height started to fall markedly. At 7 years of age, the mean height for boys with MPS II corresponded to $-1.4$ SD of the mean height for age-matched controls. After 8 years of age, the mean height for patients was below $-2$ SD of the mean for age-matched controls. The mean height for MPS II at 18 years of age or older was $127.2 \pm 8.5$ cm ($n = 12$), resulting in difference of 43.6 cm compared to the mean for the age-matched controls. This value corresponded to $-7.5$ SD of the age-matched Japanese mean. Short stature was commonly observed in spite of attenuated or severe phenotype and there was no statistical difference by severity of CNS involvement through all ages (severe vs. attenuated birth length; $50.9 \pm 2.3$ cm vs. $50.6 \pm 1.4$ cm at 18 years of age; $127.5 \pm 10.6$ cm vs. $127.1 \pm 8.7$ cm).

**Height velocity**

Height velocity was average during the first 4 years of life and thereafter declined rapidly compared with that for healthy children (Fig. 126.4). We observed a slow incremental change from 5 to 15 years of age. MPS II patients nearly stopped growing by age 10.

**Weight**

The mean birth weight for Japanese MPS II patients was $3.34 \pm 0.42$ kg ($n = 42$) which corresponded to $+0.9$ SD for boys (mean 3.0 kg) on the Japanese standard growth charts. Over 40% of all patients weighed more than the 90th percentile (3.51 kg) at birth and 19.0% weighed more than the 97th percentile (3.79 kg). Thus, the mean birth weight for MPS II patients was heavier than that for control newborns. Heavy birth weight has also been described previously in the severe form of MPS...
I, IVA, and VI (Polgreen et al., 2008, see Sections 126.3 and 126.4). The mean birth weight was not significantly different between patients with the attenuated or the severe form of the disease. The mean weight of MPS II patients was kept above 2 SD of the mean for age-matched controls until 6 years of age. At the age of 2.5 years, the difference between patients and age-matched controls was the highest (+4.9 SD) (Fig. 126.5). Around 25% of MPS II patients weighed above 2 SD of the mean between 5 and 8 years. The mean weight remained heavier until 8 years of age compared with that for age-matched control population. Between 9 and 13 years of age, the weight for around 90% of affected children remained between ±2 SD of the mean. After 14 years of age, the mean weight for over 80% of patients remained below −2 SD of the mean for age-matched controls.

At 18 years or older, the mean weight for MPS II patients was 38.6 ± 8.4 kg, resulting in below −2 SD of the mean for age-matched controls. We have also established age-dependent SD curve of the mean height and weight, compared with the aged-matched controls (Fig. 126.6). SD score of the mean MPS II patient weight to the age-matched control was disproportionally higher than that of the mean height through almost all ages. From birth to 8 years of age, SD score of the weight remained positive, while SD score of the height stayed positive only until 5 years of age. After 5 years of age, SD score of height fell down markedly, indicating early impairment compared with weight.

**Body Mass Index (BMI)**

BMI was calculated by dividing the weight by the square length or height (kg/m\(^2\)). BMI for MPS II patients over 18 years of age was 24.09 ± 3.71 kg/m\(^2\). In Japanese population, BMI of above 25 is indicated as obesity. Fifty percentage of the patients of 18 years of age and older had BMI between 25 and 30 (Fig. 126.7). None of the patients had BMI of over 30. These findings suggested that Japanese MPS II had a tendency to obesity, although there was no marked obese case.
**126.3 Mucopolysaccharidosis IVA (Morquio A Syndrome) (OMIM 253000)**

MPS IVA is an autosomal recessive disorder in which affected individuals lack the enzyme N-acetylgalactosamine-6-sulfate sulfatase (GALNS). This enzyme hydrolyzes the sulfate moiety of KS and C6S. In the absence of this enzyme, the stepwise degradation of KS and C6S is blocked, resulting in the intracellular accumulation of the respective GAG in the lysosomes of a wide range of tissues. Incidence of MPS IVA disease is approximately 1 in 250,000 live births but the incidence varies widely among countries (Applegarth et al., 2000; Baehner et al., 2005; Lowry et al., 1990; Meikle et al., 1999; Poorthuis et al., 1999). There are several studies that have documented the incidence of MPS IVA; the highest is 1 in 76,000 live births in Northern Ireland (Nelson, 1997), and
the lowest is 1 in 450,000 live births in Portugal (Pinto et al., 2004). The concept of a founder effect accounts for the discrepancy of the incidence in different ethnic populations.

### 126.3.1 Clinical Aspects

Affected infants seem normal at birth but will progress to an advanced stage of the disease within a few years. Over 70% of patients affected with MPS IVA have initial clinical manifestations within the first 2 years of life, although the formal diagnosis is usually delayed until about 2 years later (Montaño et al., 2007b). Children with MPS IVA exhibit heterogeneity in their phenotypes from attenuated features to severe systemic bone involvement. Skeletal abnormalities observed during early childhood include pectus carinatum, abnormal gait short trunk dwarfism, odontoid hypoplasia, kyphosis, scoliosis, genu valgum, coxa valga, and hypermobility of joints (Fig. 126.8). Lower spine radiographs of a patient at day 1 showed suspected anterior beaking of the lumbar vertebrae as well as minor anomalies on the phalanges that suggested a skeletal dysplasia. Subsequent radiographs showed progression of the anterior beaking sign, progressive kyphosis, platyspondyly, and irregularities of the vertebral bodies, which are signs characteristic of MPS, particularly of MPS IVA syndrome (Fig. 126.9) (Ohashi et al., 2009).

Generally, MPS IVA patients exhibiting a severe phenotype do not survive beyond the second or the third decade of life. In contrast, patients with an attenuated phenotype have been reported to survive into the seventh decade of life (Montaño et al., 2007b). Surgical interventions may be required to improve the quality of life of the patients. A recent study showed that on average, by 5 years of age, MPS IVA patients often require surgical procedures such as adenoidectomy and tonsillectomy. Thereafter, at 10 years of age, the patients undergo major surgical operations in neck, hip, knee, and leg regions (Montaño et al., 2007b).
126.3.2 Growth

Short stature is a critical feature of MPS IVA. The growth retardation of children with classical MPS IVA starts in early childhood and their growth nearly stops around 7 or 8 years of age, although some patients with an attenuated phenotype continue growing into their teens (Montañó et al., 2007b) or even have a normal height (Beck et al., 1986; Montañó et al., 2007a). The current criteria to determine the clinical severity in MPS IVA are based on growth and final height unlike other types of MPS. The assessment of physical activity and growth of MPS IVA patients is essential for monitoring disease activity, progression, and response to treatment.

This study was based on the data obtained from 388 MPS IVA patients enrolled from 45 countries. Height ($n = 2,038$) and weight ($n = 1,779$) measurements from 193 girls and 195 boys with MPS IVA were collected. The measured value for height in patients over 18 years was considered unchanged. Therefore, the data from MPS IVA patients over 18 years of age were grouped as data at 18 years. The obtained reference curves were compared with those of healthy children provided by the CDC.

Ethnic background of the studied population was predominantly as follows: Caucasian (70%), Hispanic (11%), Asian (10%), black (1%), and others (2%).
Fig. 126.9 Lateral view of progressive changes of the spine with age in the patient (copyright permission from International Morquio Organization). 1 day: A sacral dimple was noted at the delivery and suspected anterior beaking at the level of L2 was seen. 2 months: The anterior beaking was more prominent at the level of L2 with kyphosis. 15 months: Flaring of the anterior lateral ribs was observed. Kyphosis centered at L2 and flared-shaped anterior beaking of the vertebral body were marked. 32 months: Accentuated dorsal thoracolumbar kypholordosis with gibbous deformity was remarkable. Advanced platyspondyly, irregularity, and anterior beaking of the vertebral bodies characteristic of Morquio syndrome were prominent

126.3.3 Length and Height

The mean of birth length for boys and girls was 52.4 cm (n = 154) and 52.1 cm (n = 127), respectively, which corresponds to +0.9 SD for boys and +1.1 SD for girls on the CDC growth charts (Fig. 126.10). At 1 year of age, the mean height for boys and girls was 78.1 ± 5.6 and 78.3 ± 3.0 cm, respectively, which corresponds to +0.85 SD for boys and +1.6 SD for girls. At 1 year of age, the mean height of boys and girls with MPS IVA closely corresponded to that of the normal population (Fig. 126.11). After this age, the mean height of both genders started to fall markedly below the −2 SD value. The mean height for males and females at 18 years of age was 119.3 ± 22.6 cm (n = 116) and 113.5 ± 23.1 cm (n = 177), resulting in a difference of 56.8 and 49.6 cm, respectively, compared to the mean height for the age-matched controls. These values correspond to −8.0 SD and −7.7 SD of the height for normal healthy males and females (Fig. 126.11).

126.3.4 Height Velocity

The height velocity curve (mean) of MPS IVA patients is depicted in Fig 126.12. The height velocity for boys with MPS IVA was greater during the first 6 months of life than that for age-matched
**Fig. 126.10** Birth length of boys and girls with MPS IVA disease (copyright permission from International Morquio Organization)

**Fig. 126.11** Growth charts for length/height (cm) of boys (a) and girls (b) with MPS IVA from birth to 18 years of age (copyright permission from International Morquio Organization). The *dotted line* shows the 50th centile values for normal boys and girls from CDC charts.
controls and declined thereafter rapidly. The growth spurts for MPS IVA patients were reduced compared to those for normal healthy controls. There were two accelerated peaks between 10 and 11 years of age, and between 16 and 17 years of age. The height velocity for girls with MPS IVA was greater during the first 6 months of life than that for age-matched controls and dropped after 6 months old. Subsequently, we observed the growth spurt between 11 and 12 years of age. The growth pattern of MPS IVA patients is characterized by impaired growth velocity at least after 1 year of age. The difference in the pattern of the velocity at certain ages in comparison with that of normal controls could be corrected by adding more data to increase the size of the study group. The individuals with MPS IVA reached their final height approximately at 11 years of age for males and 12 years of age for females. We observed taller final heights for both genders at 18 years of age, since the continually increasing height data from attenuated MPS IVA patients contributed disproportionately to the total. This study also showed that individuals with MPS IVA had a reduced pubertal growth spurt, contributing to marked short stature. Some studies of other genetic diseases showed the same phenomena (Myrelid et al., 2002).

126.3.5 Weight and BMI

The mean of birth weight for boys and girls was 3.56 kg \((n = 176)\) and 3.50 kg \((n = 149)\), respectively, while the mean of birth weight for normal healthy boys and girls was 3.5 and 3.4 kg, respectively, on the CDC growth charts (Fig. 126.13). Thus, the birth weight of MPS IVA patients
was a little heavier than that of normal controls. The weight of children with MPS IVA up to age 12 years was within the $-2$ SD of the normal children. Thereafter, most children with MPS IVA gained weight gradually. The mean weight of males and females with MPS IVA at 18 years was $36.5 \pm 13.2$ kg ($n = 96$) and $35.2 \pm 13$ kg ($n = 108$), respectively. These values corresponded to $-3.5$ SD and $-3.1$ SD of the weight for age-matched normal males and females (Fig. 126.14).

We have established age-dependent $Z$ score curve of the mean height and weight, compared with the aged-matched controls (Fig. 126.15). $Z$ score of the mean MPS IVA patient weight to the age-matched control was higher than that of the mean height through almost all ages in both genders. From birth to 1 or 2 years of age, $Z$ score of the weight for male or female patients remained positive, while $Z$ score of the height stayed positive until 1 year of age. After 1 year of age, $Z$ score of height fell down markedly, indicating early impairment compared with weight.

The BMI for MPS IVA males and females over 18 years of age was $24.7 \pm 6.1$ and $25.6 \pm 5.4$ kg/m$^2$, respectively. These values corresponded to $+1.3$ SD and $+1.9$ SD of the BMI for age-matched normal males and females, respectively. BMI above the 95th centile indicating overweight ($34.7$ and $34.4$ kg/m$^2$ for males and females, respectively) was observed in $6.8\%$ of the males and $5.4\%$ of the females with MPS IVA of 18 years of age and older (Fig. 126.16). BMI above the 85th centile ($31.9$ and $32.4$ kg/m$^2$ for males and females, respectively), indicating patients at risk of overweight, was observed in $15.2\%$ of the males and $9.5\%$ of the females with MPS IVA of 18 years of age and older.

Although the mean weight for MPS IVA patients over 18 years was considerably lighter than that for the normal population, $6.8$ and $5.4\%$ of males and females, respectively, were overweight in the MPS IVA population. We also found that most wheelchair-bound patients were at risk of overweight or indeed obese. BMI is considered the best available weight–stature index in both children and adults, independent of stature, correlation with body fat, and prediction of mortality (Nysom et al., 2001). It is important to compare the measurements of BMI with adequate sex- and age-specific
**Fig. 126.14** Body weight (kg) of boys (a) and girls (b) with MPS IVA from birth to 18 years of age (copyright permission from International Morquio Organization). The *dotted line* shows the 50th centile values for normal boys and girls from CDC charts.

**Fig. 126.15** Z score curve of height and weight of patients with MPS IVA (copyright permission from International Morquio Organization). The *black dotted line* shows Z score of the mean height of male MPS IVA to that of normal boys from CDC data. The *solid black line* reveals Z score of the mean weight of female MPS IVA to that of normal girls. The *grey dotted line* shows Z score of the mean height of female MPS IVA to that of normal girls from CDC data. The *solid gray line* reveals Z score of the mean weight of male MPS IVA to that of normal boys.
Fig. 126.16  Body mass index [weight (kg)/height$^2$ (m$^2$)] of boys (a) and girls (b) with MPS IVA from birth to 18 years of age (copyright permission from International Morquio Organization). The dotted line shows the 50th centile values for normal boys and girls from CDC charts.

Reference values. In this study, we observed that there was an upward shift of the mean of BMI for both males and females with MPS IVA when compared to the normal population.

126.3.6 Height, Weight, and Physical Activity

Correlation between final height and physical activity of MPS IVA patients was analyzed based on the absence or the presence of major surgical procedures. Presence of surgical procedures was independent of the height of the patients. We did not observe significantly increased heights in those patients with fewer surgical procedures (data not shown).

There was a tendency for patients with heights between 80 and 100 cm to have a reduced capacity for walking distance between 0 and 400 m regardless of the presence or the absence of a history of surgical intervention(s). MPS IVA patients over 130 cm tall, who had undergone surgery, walked a shorter distance (0–200 m) than those without any history of surgery (over 800 m). Walking aid was required in almost all MPS IVA patients, regardless of height and weight. Eighty-five percent of patients who required walking aid underwent surgeries. Use of a wheelchair was broadly distributed among MPS IVA patients with widely ranging statures. There were no wheelchair-bound cases among over 130 cm patients who had not undergone surgery. All bedridden MPS IVA patients were associated with a history of surgical procedures.

Over 80% of overweight MPS IVA patients (above 85th centiles termed as “a risk of overweight”) had limited physical activity (walking distance was between 0 and 200 m). In addition, two-third of wheelchair-bound males and over half of wheelchair-bound females were at risk of overweight. We associated the physical condition of the patients, as a marker of health, with their growth. There was a tendency for patients with short stature to walk a shorter distance when compared to those with...
greater stature. In addition, patients with greater stature who underwent surgical procedures could walk less when compared to those who did not have any kind of surgical procedure. Since it is known that lack of exercise could lead to psychological and physical setbacks in any individual, monitoring exercise is critical for patients with generalized bone dysplasia like MPS IVA patients.

### 126.3.7 Classification of Phenotype

The newborn length and weight in MPS IVA appear similar or even slightly increased compared to those of the normal population. This finding makes diagnosis and prognosis of MPS IVA at birth a difficult task unless some bone deformities or short stature associated with a skeletal dysplasia is recognized.

Establishment of growth charts for both genders indicated that we also have to take into consideration the gender to classify MPS IVA patients. The mean final height for females is shorter than that for males. The classification of phenotype on MPS IVA should be performed based upon the standard growth chart for each gender of MPS IVA patients. According to the isopleth upon which the patient falls, patients above the 90th centile on the growth chart for each gender are more likely to be defined as attenuated.

### 126.4 Mucopolysaccharidosis VI (Maroteaux–Lamy Syndrome) (OMIM 253200)

MPS VI is a lysosomal storage disease in which the deficiency of the enzyme N-acetylgalactosamine 4-sulfatase (aryl sulfatase B) affects the degradation of the GAG, DS (Neufeld and Muenzer, 2001). Partially degraded GAG accumulates in lysosomes in various tissues, causing a chronic progressive disorder which impairs the quality of life and reduces the life span (Giugliani et al., 2007).

#### 126.4.1 Clinical Aspects

Clinically, MPS VI is characterized mainly by short stature with facial, ocular, osteo-articular, cardiac, and pulmonary manifestations (Neufeld and Muenzer, 2001). Accelerated growth has been reported in the first years of life in MPS VI with advanced bone maturation at birth, followed by slowing growth rate and growth failure noted after 2 years of age (Heron et al., 2004), a pattern already reported in some skeletal dysplasias (Hoover-Fong et al., 2008; Montaño et al., 2008).

Inflammatory response, cell dysfunction, and death, secondary to abnormal GAG storage in chondrocytes, may be the cause of growth plate failure in MPS VI (Simonaro et al., 2001, 2005, 2008).

#### 126.4.2 Growth

An observational study in 121 untreated MPS VI patients, a large sample considering the rarity of this condition, demonstrated mean height of 115.2 ± 26.1 cm and median height of 103.7 cm with a range of 80.0–169 cm (Swiedler et al., 2005). The large difference between the mean and median values was attributed to the minority of taller subjects with slowly advancing disease.
The Brazilian sub-sample of this study reported in detail the severe impact of the disease on height and weight as age advances (Azevedo et al., 2004). The main data obtained on growth could be observed in Figs. 126.17 and 126.18.

### 126.4.3 Height

Height, as an indicator of skeletal development, was examined as a function of age and stratified by urinary GAG levels and gender (Swiedler et al., 2005). High urinary GAG levels corresponded to low height at all ages, while individuals with lower GAG levels (<100 μg/mg creatinine) were closer to the lower range of normal height for their age (Fig. 126.19).
Fig. 126.19 Height versus age stratified by urinary GAGs in MPS VI subjects. Patients were classified into three groups, according to urinary GAG levels (below 100, between 100 and 200, and above 200 μg/mg creatinine). The normal growth curves are represented by the 50th centile (solid lines) or 3rd centile (broken line), obtained from the CDC (http://www.cdc.gov) (reproduced with permission from Swindler et al., 2005).

126.4.4 Genotype and GAG Correlation

In a subsequent report which included mutational data from the Swiedler et al. (2005) study, Karageorgos et al. (2007) established a relationship between genotype and urinary GAG levels (Fig. 126.20). The most common mutation found in the sample (p.Y210C, detected in 18% of the MPS VI patients) is associated with a level of urinary GAG below 100 μg/mg creatinine and with an attenuated phenotype, while patients with high urinary GAGs were found to have mutations associated with the rapidly progressing form of the disease.

Taken together, this data indicates that there is a correlation between genotype and urinary GAG levels, and between urinary GAG levels and phenotype, with a more severe picture on patients with higher urinary GAG levels.
126.4.5 Impact of ERT on Growth

The skeletal manifestations of MPS VI appear difficult to treat, given the inability of bone marrow transplantation to reverse established skeletal dysplasia or promote growth in those individuals treated after growth has stopped (Herskho vitz et al., 1999). The effect of ERT, reported in several clinical trials (Harmatz et al., 2005, 2006, 2008), was analyzed by treatment week and longitudinal modeling and demonstrated significant increase in height and growth rate in MPS VI patients receiving long term ERT (Decker et al, 2010). It was shown that this effect was more significant in patients who start therapy at a younger age, as supported by the sibling cases presented by McGill et al. (2006). In his report, two siblings were followed for the same period after starting ERT. The sibling who started treatment a few months after birth had a much better outcome regarding growth and skeletal disease compared to the sibling who started treatment at 3 years and 6 months of age. Interestingly, animal models of MPS VI have demonstrated improved growth plate structure with early initiation of ERT (Byers et al., 1997).

In conclusion, growth is a serious problem for most MPS VI patients, with short stature being more severe in patients with higher urinary GAGs and a genotype with greater impact on the enzyme level and/or the activity. Although this manifestation of the disease is probably difficult to revert, there are indications that treatment with ERT, especially if introduced early, could favorably change the final outcome.

126.4.6 Etiology of Growth Impairment

In some genetic diseases, hypogonadism, insufficient GH secretion, thyroid hormone, sex hormones, IGF-1, or other growth factors can explain reduced pubertal growth in patients. These are all critical for normal growth and development. However, in MPS patients, no statistical analyses of these growth-promoting factors with age have been performed to prove that there is evidence of deficiency or reduction in MPS patients. Low IGF-1 levels have been reported in MPS II (Toledo et al., 1991).

Overall, the current literatures suggest that pituitary dysfunction, hypothyroidism, low IGF-1 and GH, and pubertal disruption may be associated with MPS in some cases and therefore may contribute
to the short stature. Growth impairment in MPS II patients was slower and milder compared with that in MPS IVA patients. MPS II patients with either attenuated or severe form have nearly the same short stature and there was no correlation with severity of CNS impairment. MPS IVA patients showed broader severity in growth development and skeletal abnormalities. By growth impairment, the clinical severity can be classified. Most KS is synthesized in cartilage cells of growth plate regions and undegraded KS will be stored in affected cartilage cells in MPS IVA, resulting in malfunction of cells and apoptosis. Devastating destruction of cartilage cell layers largely contributes to growth impairment. On the other hand, primary GAGs such as DS and HS in MPS II or DS in MPS VI were accumulated in liver, spleen, kidney, skin, pituitary gland, thyroid gland, and testes. These GAGs may provide direct impact on not only growth plate region but also endocrine system. Understanding of etiology in growth impairment will require further investigation.

126.4.7 Disproportional growth impairment

MPS patients have disproportional defect in height growth compared with body weight, resulting in increase of BMI and relative overweight. MPS patients with marked short stature should avoid obesity. There is some consensus that, in addition to the risks posed by obesity in the general population, extra weight in those with severe bone dysplasia may cause stress on susceptible bones and joints, resulting in premature neurological and orthopedic complications. Joints in MPS patients are already impaired mainly from epiphyseal dysplasia caused by incomplete endochondral ossification of epiphyseal cartilage. Cartilage with an abnormal ossification process is fragile, and joints tend to degenerate rapidly and develop early arthrosis leading to surgical interventions such as joint replacement (Kanazawa et al., 2001), especially in the weight-bearing lower extremities. In general, overweight is a risk factor that will contribute to the deterioration of MPS patients’ health.

126.5 Clinical End Point

Advanced treatments for MPS are currently being developed including enzyme replacement therapy. Such treatments may improve the quality of life by slowing down the underlying disease process of MPS and preventing further damage of targeted organs. The efficacy of the treatment has to be evaluated carefully by monitoring several clinical end points. The evaluation of growth pattern before and after treatment will be one of the important end points.

Individual disease-specific charts can be used to evaluate the spontaneous growth pattern in each type of MPS population. Growth charts specific for children with MPS are therefore important tools in medical surveillance as well as in the monitoring of growth-promoting treatments (Table 126.1).

126.6 Conclusion and Future Perspective

Understanding the impact of growth on health and physical condition will require more careful measurements and a larger sample size to demonstrate more statistically significant results. Currently there are no standardized measurement techniques to assess growth in patients with MPS disease by each individual physician. A board of experts from the field of MPS research will review the findings. Nevertheless, we feel that the current data accumulated for growth are suggestive and worthy of correlation between growth and physical activity in individual MPS patients.
In conclusion, children with MPS have poor growth compared with typical children. We have reviewed growth curves for children with MPS II, IVA, and VI and correlated growth with markers of health and physical condition. Taller children with MPS IVA had better health and physical status compared to shorter children. However, we did not observe that taller children with MPS II had better clinical phenotype in CNS involvement compared to shorter children. Hence, each type of MPS has a different aspect in clinical severity and its consequence. Further studies are needed to corroborate these findings and to evaluate whether specific interventions can improve growth, as well as health and physical activity.

**Summary Points**

- **Mucopolysaccharidoses (MPS):** The MPS are a group of inherited metabolic diseases caused by the absence or malfunction of certain enzymes needed to break down molecules called glycosaminoglycans (GAGs) – long chains of sugar carbohydrates in each of our cells that help build bone, cartilage, tendons, corneas, skin, and connective tissue.
- **Hunter syndrome:** Hunter syndrome is one of the MPS diseases also known as MPS II. It takes its name from Dr Charles Hunter, a physician in Manitoba, Canada, who first described two brothers with the disease in 1917. MPS II patients have a wide range of symptoms that vary in severity.
- **Morquio syndrome:** Morquio syndrome is one of the MPS diseases and is also known as MPS IV. MPS IV takes its name from Dr Luis Morquio, a pediatrician in Montevideo, Uruguay, who in 1929 described a family of four children affected by this condition. MPS IV patients have unique systemic bone disease without intellectual damage.
- **Maroteaux–Lamy syndrome:** Maroteaux–Lamy syndrome is one of the MPS diseases and is also known as MPS VI. It takes its name from two French doctors, Dr Maroteaux and Dr Lamy, who first described the condition in 1963. MPS VI patients have organ enlargement and unique systemic bone disease.
- **Enzyme replacement therapy (ERT):** ERT is a medical treatment replacing an enzyme in patients in whom that particular enzyme is deficient or absent. Usually this is done by giving the patient an intravenous (IV) infusion containing the enzyme. Enzyme replacement therapy does not “treat” the underlying disease, only the symptoms.
- **Hematopoietic cell transplantation (HCT):** HCT is the transplantation of blood stem cells derived from the bone marrow or blood. HCT is a medical procedure in the fields of hematology and
oncology, most often performed for people with diseases of the blood, bone marrow, or certain types of cancer.

- **Kyphoscoliosis**: It describes an abnormal curvature of the spine in both a coronal and a sagittal plane. It is a combination of kyphosis and scoliosis.

- **Genu valgum**: Genu valgum, also known as knock-knee, is a condition where the knees angle in and touch one another when the legs are straightened. Females have a greater static genu valgum compared to males.

- **Growth charts**: Growth charts show health-care providers how children are growing compared with other children of the same age and gender and are a standard part of any checkup. They allow doctors to see the pattern of height and weight gain over time, and whether children are developing proportionately.

- **Glycosaminoglycan (GAGs)**: GAGs are also known as mucopolysaccharides and are long unbranched polysaccharides consisting of a repeating disaccharide unit.

- **Z score**: In statistics, a Z score (standard score) indicates how many standard deviations an observation is above or below the mean. It is a dimensionless quantity derived by subtracting the population mean from an individual raw score and then dividing the difference by the population standard deviation.

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