

## Review Article

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# Growth patterns and the use of growth hormone in the mucopolysaccharidoses

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**Abstract.** Short stature is characteristic of patients with mucopolysaccharidosis (MPS) diseases. For children with skeletal dysplasias, such as MPS, it is important to know the natural history of growth. An understanding of the natural growth pattern in each MPS disease provides a measurement to which treatments can be compared, as well as data which can help families and providers make individualized decisions about growth promoting treatments. Multiple advancements have been made in the treatment of MPS with both hematopoietic cell transplantation (HCT) and enzyme replacement therapy (ERT). The long term benefit of these treatments on growth is unknown. This article will review the published data on growth in children with MPS, and describe preliminary data on the use of human growth hormone (hGH) in children with MPS.

**Keywords:** Growth, growth hormone, mucopolysaccharidoses, MPS, endocrine disease

## 1. Introduction

The mucopolysaccharidoses (MPS) are a group of diseases characterized by various deficiencies in enzymes required for degradation of complex carbohydrates. The enzymatic deficiencies result in the lysosomal accumulation of dermatan sulfate (DS), heparan sulfate (HS), and/or keratan sulfate (KS) in various tissues resulting in multi-system complications [65,98]. The multiple advancements that have recently been made in the treatment of MPS, in both hematopoietic cell transplantation (HCT) and enzyme replacement therapy (ERT), have significantly improved the duration and quality of life for these children. The long-term benefit of these treatments, however, is largely unknown. It seems that liver, spleen, respiratory, and cardiovascular complications of these diseases are significantly diminished [15–17,23,36,38,39,50,60, 87,89,94], but that the musculoskeletal, growth, and

endocrine abnormalities are not entirely alleviated by these treatments [30,49,69,97].

Short stature is characteristic of patients with MPS, and is likely secondary to a combination of structural, metabolic, and endocrine abnormalities. The characteristic skeletal abnormalities of MPS (e.g. kyphoscoliosis and genu valgum) limit growth and adult height. However this does not entirely explain the short stature since it is found in children with MPS 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 also be related to abnormalities of the growth plate which include decreased matrix deposition with impaired osteoblast function, hypertrophic chondrocytes, disordered growth plate cellular structure, and GAG accumulation in the growth plate (Fig. 1) [1,57,66,78,84]. Bone formation has been shown to improve in the feline model of MPS VI when treated with ERT in a dose dependent manner [20], however no data are available in humans.

We have previously shown a very high prevalence of later growth failure in children with MPS IH treated with HCT suggesting a lack of penetration of enzyme

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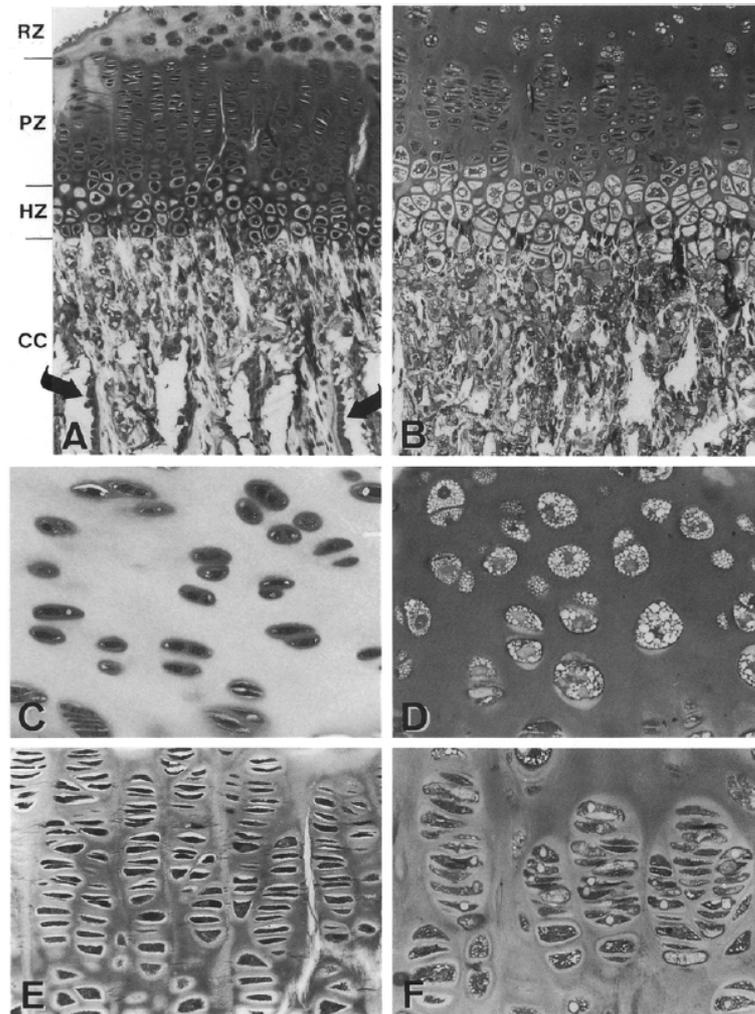


Fig. 1. (A) A longitudinal histological section of a decalcified epiphyseal growth plate from a control cat with clearly defined growth zones. In the calcified cartilage zone, osteoblasts line the trabeculae (arrows). RZ (resting zone), PZ (proliferative zone), HZ (hypertrophic zone), CC (calcified cartilage). Magnification  $\times 150$ . (B) A midline longitudinal histological section of a decalcified epiphyseal growth plate from a cat with MPS VI. Note that the different zones are distinguishable, but there are clear differences in the organization and structure of tissue and cells compared with the control cat of A. There is a disruption of the proliferate zone, and a loss of columnation of the hypertrophic zone. Magnification  $\times 150$ . (C) A higher magnification of normal chondrocytes in the resting zone of the control cat of A. Magnification  $\times 400$ . (D) A higher magnification of the resting zone of an MPS VI-affected animal. Note the larger, swollen, vacuolated cells with clumped cytoplasm that is separated from the plasma membrane, and indistinct nucleus. Magnification  $\times 400$ . (E) A higher magnification of the proliferative zone of a control animal. Note the well-defined columns with an even height and number of cells. Individual cells have some normal degree of flatness with internal spaces filled with cytoplasm, and a clearly distinguishable nucleus. Magnification  $\times 400$ . (F) A higher magnification of the proliferative zone of an MPS VI cat. The columns are poorly organized, with fewer cells per column. Note the flattened cells showing a condensed cytoplasm separated from the plasma membrane, and an indistinct nucleus. Magnification  $\times 400$ . (From Abreu et al. Growth Plate Pathology in Feline Mucopolysaccharidosis VI. *Calcif Tissue Int.* 57 (1995), 185–190, with permission.).

into the growth plate [69]. In addition, the skeletal and joint abnormalities have also been shown to persist and even worsen with time since HCT [30,97]. Lysosomal GAG accumulation has been documented in the pituitary gland, thyroid gland, and testes of children with MPS II [64,67], and in ovarian tissue of a murine model of MPS VII [86]. Growth hormone, thyroid hormone,

and sex steroids (estrogen, testosterone) are all critical for normal growth and development. Low insulin-like growth factor-1 (IGF-1) levels have been reported in three brothers with MPS II [90]. Precocious puberty has been described in MPS IIIA [91], and we described hypothyroidism, growth hormone (GH) deficiency, low IGF-1, and precocious puberty in children with MPS

IH after HCT [69]. Precocious puberty may be related to hypothalamic or pituitary damage, in particular after total body irradiation (TBI) used prior to HCT, and is particularly detrimental to adult height due to a rapid closure of the growth plates. In summary, current literature suggests 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.

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. 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 a measure to which new treatments can be compared. 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  $-6$  standard deviations below the mean height for age and gender. Short stature this severe limits activities of daily living, and can negatively impact social development, socio-economic status, and career advancement [33,74,103]. This article will review the current published data on growth in children with MPS, and describe preliminary data on the potential use of human growth hormone (hGH) in children with MPS.

## 2. Growth

### 2.1. MPS I

#### 2.1.1. Growth in MPS I after HCT

Hurler syndrome, or mucopolysaccharidosis type IH (MPS IH), is an autosomal recessive, lysosomal storage disease caused by deficiency of alpha-L-iduronidase, an enzyme which is required for the breakdown of the glycosaminoglycans (GAG) heparan and dermatan sulfate [9]. Clinically, MPS IH is characterized by short stature, coarse facies, cognitive and gross motor delays, corneal clouding, dysostosis multiplex, cardiac manifestations, and hepatosplenomegaly [8,27,65,68,98]. Dysostosis multiplex is a constellation of skeletal abnormalities including kyphosis, scoliosis, hip dysplasia, and genu valgum. MPS IH is typically diagnosed in patients less than two years of age.

Without treatment, children with MPS IH typically die by 10 years of age due to cardiac or respiratory complications [65,98]. Currently, most children with MPS IH are treated with HCT [23,36,50,87,94]. HCT as an intervention, however, compounds the problem of short stature. HCT has been associated with growth suppression, growth hormone deficiency, abnormal gonadal and thyroid function, and damage to the epiphyseal growth plate, pituitary gland and hypothalamus [10,11,18,31,32,43,52,73,82], all potential causes of short stature. With HCT, children with MPS IH are living into their adult years and therefore determining long-term outcomes and complications has become clinically important. Early diagnosis and replacement of hormonal deficiencies are critical for optimizing growth and development. While many studies have examined long-term growth for other conditions following HCT [18,31,32,43,52,73,82], there are few growth data specific to patients with MPS IH children after HCT [69,87,94].

Polgreen et al. found a prevalence of short stature in children with MPS IH after HCT to be 71% at the most recent evaluation. The growth patterns for both genders demonstrated a progressive falling behind relative to the CDC reference data (Fig. 2). Later age at HCT and exposure to TBI were associated with an increased prevalence of short stature. By 10 years of age, mean height SD decreased to  $-3.2 \pm 1.6$  SD and the prevalence of short stature increased to 87% ( $n = 13$  of 15). Short stature was diagnosed in 46% of children who had a cord blood donor, 72% and 88% (related and unrelated, respectively) of children who received bone marrow. This seems to suggest improved growth in children treated with cord blood HCT; however this difference was compounded by the fact that the length of follow up was shorter in these children compared to those with other donor sources. This association was not statistically significant when adjusting for the age at last height evaluation. The prevalence of short stature in children with MPS IH after HCT was quite high compared to that found in other studies of patients who received HCT for conditions other than MPS IH [11, 52,82]; 14–31% of patients in these reports had short stature at last follow-up, compared to 71% with short stature in MPS IH patients.

Progressive growth failure in children with MPS IH after HCT was also reported by Vellodi et al. [94]. They found that the mean height fell beneath the normal range for age around 8 year of age. They also measured sitting heights and leg lengths; their data suggested that the decrease in sitting height accounted for the majority

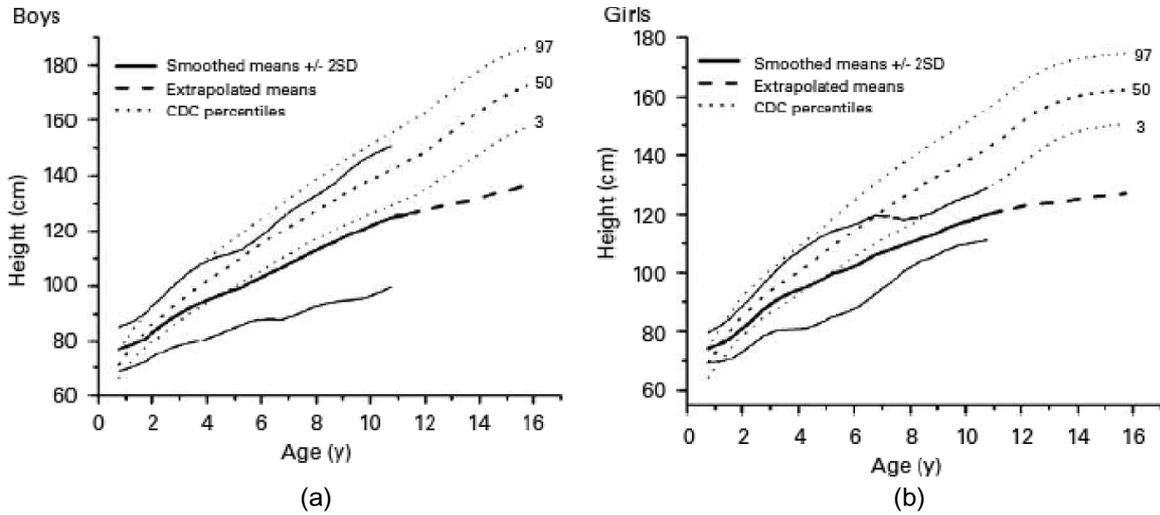


Fig. 2. Growth patterns of boys (a) and girls (b) from time of hematopoietic stem cell transplantation (HSCT) to time of last follow-up visit superimposed on standard Centers for Disease Control and Prevention (CDC) percentiles for height by age. (From Polgreen et al. Growth and endocrine function in patients with Hurler syndrome after hematopoietic stem cell transplantation, *BMT* 41 (2008), 1005–1011, with permission).

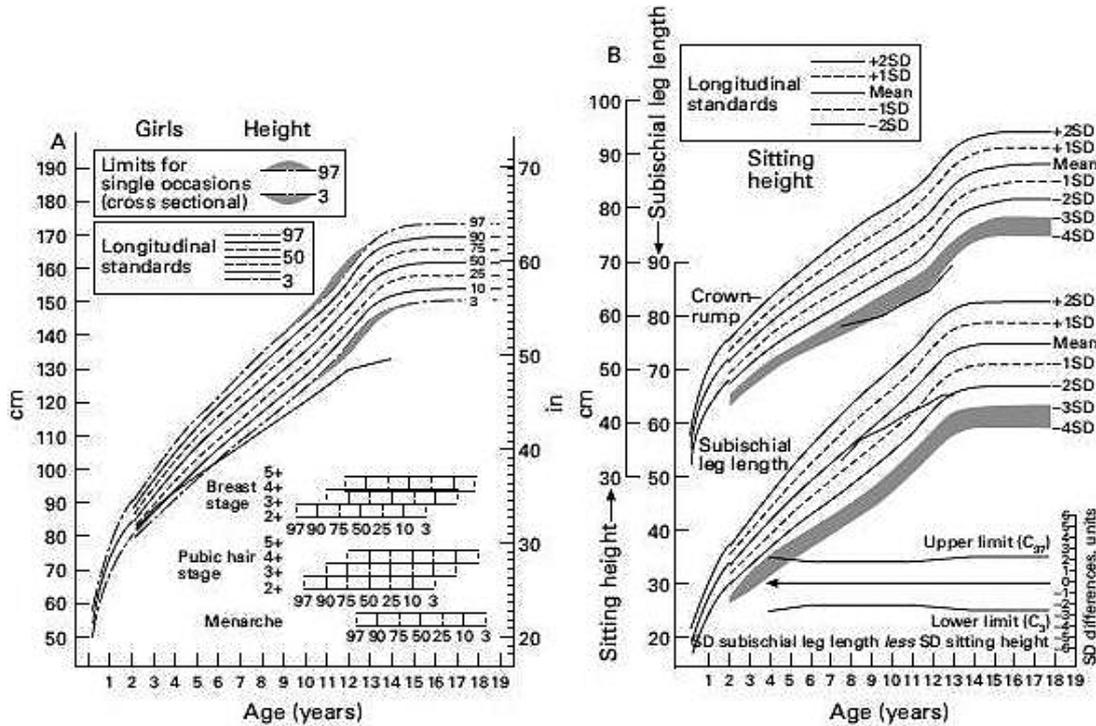


Fig. 3. Linear growth chart showing gradual falling off of height (A) and sitting height and subischial leg length: note the relative position of the latter (B). (From Vellodi et al. Bone marrow transplantation for mucopolysaccharidosis type I: experience of two British centres. *Arch Dis Child* 76 (1997), 92–99, with permission).

of decreasing growth velocity. Although total body irradiation (TBI) has been associated with poor spine growth [40,54], only 1 subject in the study by Vellodi et al. had received TBI. Therefore, it appears to be the

persistence of MPS skeletal disease which resulted in the decreased sitting height.

Another study of outcomes in MPS IH after HCT was published by Staba et al. [87] They found normal

Table 1

Height and weight growth. (From Sifuentes et al. A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. *Molecular Genetics and Metabolism* **90** (2007), 171–180, with permission.)

Patient Na	Height (cm)				Weight (kg)			
	Year 0	Year 2	Year 6	%Increase	Year 0	Year 2	Year 6	%Increase
003 <sup>a</sup>	122.5	134.0	162.9	33.0	27.0	34.4	56.7	110.0
004 <sup>a</sup>	125.0	137.0	156.7	25.4	34.6	48.4	73.8	113.3
005 <sup>a</sup>	127.0	143.7	154.4	21.6	24.4	35.2	47.0	92.6
007	160.0	160.4	161.1	0.7	57.2	61.4	66.4	16.1
010	160.0	159.7	160.4	0.3	54.6	63.4	65.6	20.2
Overall Mean <sup>b</sup>	138.9 (124.8)	147.0 (138.2)	159.1 (158.0)	16.2 (26.6)	39.6 (28.7)	48.6 (39.3)	61.9 (59.2)	70.4 (105.3)

Individual data are shown for growth at baseline, 2 years and 6 years of treatment. The pre-pubertal patients 003, 004 and 005 grew 26.6% during this period whereas the older post-pubertal patients did not grow. Weight increased more than proportionally with the same pre-pubertal patients gaining 105.3% in weight. Comparison of individuals show a consistent pattern of growth over the 6-year period. Prior work had shown an increase in growth rate in the first year on therapy [45].

<sup>a</sup>Patients 003, 004, and 005 were prepubertal at the time of enrolment in the Phase 1/2 Study.

<sup>b</sup>Means shown in parentheses are for the 3 patients who were prepubertal at Baseline.

growth velocity for 1–4 years after cord blood HCT in 6 children with MPS IH, less than 7 years of age at the last follow-up, and speculated that possibly cord blood HCT resulted in improved growth after HCT. However, in the study by Polgreen et al. [69] this association was lost with increased length of follow-up. Therefore the finding by Staba et al. may be influenced by the relatively short follow up period. Currently, there are insufficient long-term data to draw definitive conclusions about the impact of donor type (stem cells versus marrow) on growth, or the expected final adult height in this population.

### 2.1.2. Growth in MPS I during ERT

Growth has also been evaluated in children with MPS I who were treated with ERT by Kakkis et al. [45]. They found that after 1 year of treatment with ERT, growth velocity increased significantly from a mean growth velocity of 2.8 cm/yr to 5.2 cm/yr, an increase that is considered significant in the pediatric growth hormone literature. Individual increase in growth velocity after 1 year of treatment with ERT ranged from 0.9 cm/yr to 5.1 cm/yr.

Long-term follow up of the impact of ERT on growth in MPS I by Sifuentes et al. [83] found a much greater improvement in growth velocity in children with MPS I who were prepubertal compared to those who were pubertal (Table 1). The three children in this study who were prepubertal at the initiation of ERT increased their height on average by 27%, compared to those who were pubertal and only increased height by 0.5%. This suggests that earlier initiation of ERT may result in improved adult height; however the number of patients was small and no long term data are currently available to confirm this. Ongoing skeletal disease and development of pituitary insufficiencies may ultimately limit

height potential unless new treatments for bone disease are developed, and early detection of endocrine disease is established in routine clinical care.

### 2.2. MPS II

Hunter Syndrome (MPS II) has generally less severe clinical features compared to MPS I. The characteristic clinical findings of MPS II are coarse features, dysostosis multiplex with severe short stature, valvular heart disease, deafness, and hepatosplenomegaly [65,101]. There are two forms of Hunter syndrome, MPS IIA and MPS IIB. MPS IIA is more severe and is characterized by progressive mental deterioration and death by the mid teens. MPS IIB is the milder form, characterized by minimal mental deterioration and survival into adulthood. Children with Hunter syndrome treated with ERT [60] seem to have improved mobility, pulmonary function, and energy level, and decrease hepatosplenomegaly [60,101].

Young et al. found that in 31 cases of mild Hunter syndrome growth velocity began to decline significantly around age 4 years resulting in short stature in 100% of the children by age 12 years (Fig. 4). No data have yet been published on growth in children with MPS II treated with ERT.

### 2.3. MPS III

Sanfilippo syndrome (MPS III) results from impaired degradation of heparan sulfate [29]. MPS III has four forms and is distinguished from the other MPS syndromes by the severity of CNS disease. The only published data on growth in MPS III is from Vellodi et al. who reported the response to treatment with HCT in two twin sisters with MPS III [93]. Their report

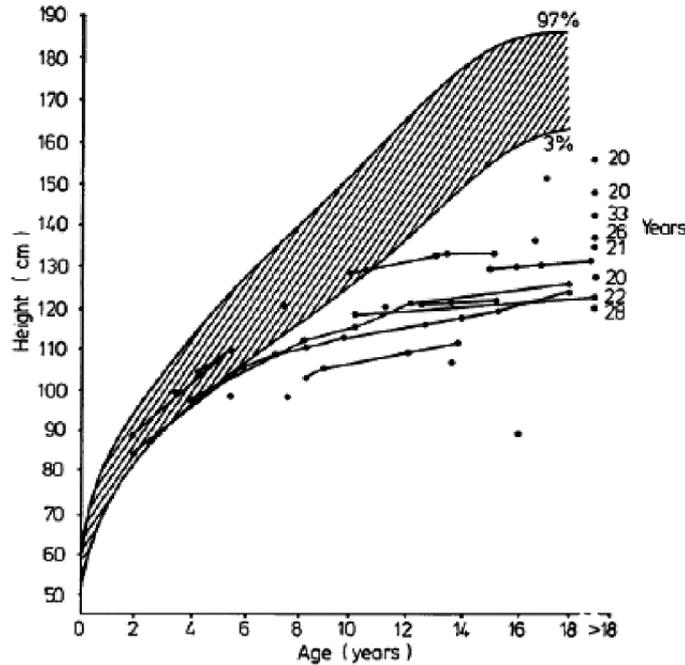


Fig. 4. Linear growth in study patients. (From Young and Harper. Mild form of Hunter's syndrome: clinical delineation based on 31 cases. *Arch Dis Child* 57 (1982), 828–836, with permission.)

followed these twin girls for 9 years after HCT and showed periods of normal growth, with periods of decreased growth. ERT is not currently available for MPS III. There are no published growth data on untreated children with MPS III.

#### 2.4. MPS IV

The International Morquio Organization Registry has accumulated a wealth of data, including growth data, in MPS IV. Morquio syndrome (MPS IV) is caused by the accumulation of keratan sulfate which results in skeletal dysplasia and short stature [59]. There are two described forms of Morquio syndrome – types A and B. Type A is most severe form. The majority of data are for type A. Montano et al. published registry results of growth in 312 children and adults with Morquio type A [59]. They found progressive growth failure in children with Morquio type A. The mean adult height for men was  $122.5 \pm 22.5$  cm and for women was  $116.5 \pm 20.5$  cm. This is significantly shorter than the mean adult height for men and women based on the CDC reference data (176.2 cm and 163.1 respectively).

Montano et al. went on to publish growth data from 354 patients with Morquio A, using a questionnaire-based longitudinal and cross sectional design [58]. They found that the mean length/height in an infant and

young child with Morquio A was similar to that of the normal population, however around 4 years of age the mean height fell below the normal range ( $< -2$  SDS) and there was progressive growth failure. This is earlier than that found in children with MPS IH and MPS II. The subjects in this study reached their final adult height at 11 years for males and 9 years for females.

#### 2.5. MPS VI

The clinical features of Maroteaux-Lamy syndrome (MPS VI) vary in severity but resemble MPS I and II with short stature, hepatosplenomegaly, dysostosis multiplex, cardiac abnormalities, and characteristic facial features. Contrary to MPS I and II, cognitive functioning in MPS VI is typically normal. MPS VI is treated with ERT which has been shown to be safe, improve mobility and endurance, and decrease urine GAG levels [38,39]. However, there are currently no reports of growth either before or during ERT in MPS VI.

### 3. Growth hormone

#### 3.1. Growth impact of human growth hGH

Recombinant hGH has been shown to be safe and effective for the treatment of short stature in various pop-

ulations, including GH deficiency, small for gestational age (SGA), Turner syndrome, Noonan syndrome, children receiving long-term glucocorticoid therapy, chronic renal insufficiency, SHOX deficiency and Leri-Weill, Prader-Willi syndrome, and idiopathic short stature [5, 15,42,56,57,64,73,88,95]. hGH has been used to treat short stature in certain populations of children with skeletal dysplasias with variable results [4,13,19,37,46, 48,72,88]. There has been concern that hGH may worsen skeletal disproportions in skeletal dysplasias; however, the reports of worsening disproportionality appear to be exclusive to children with achondroplasia [19,72, 88].

### 3.2. *Skeletal impact of hGH*

Although there are potential orthopedic complications of treatment with hGH, hGH has been shown to have beneficial skeletal and bone composition effects which may outweigh these concerns. Treatment with hGH has been shown to increase total body, lumbar, and femoral neck BMD and BMD Z-scores by DXA, decrease body fat percentage, and improve peak bone mass accrual [2,3,12,34,35,47,79,100]. A study by Lanes et al. showed an increase in lumbar spine BMD by DXA in children with idiopathic short stature (not GH deficient), who were treated with hGH [51]. This improved BMD gain is likely mediated through the increased production of insulin-like growth factor-1 (IGF-1) which has been shown in both humans and animal models to stimulate bone turnover in favor of bone formation resulting in increased BMD [3,25,28, 53,102]. GH does not appear to directly stimulate chondrocyte proliferation, rather stimulation is via IGF-1 [44].

A potential adverse effect of treatment with hGH is worsening of scoliosis and kyphosis, which are characteristic of MPS. Although it is generally thought that any growth has the potential to worsen scoliosis [26, 37], there is no clear conclusion in the literature regarding the impact of hGH on the prevalence or progression of scoliosis or kyphosis. While some researchers have found a higher than expected percentage and rate of curve progression [96], others have observed little to no progression attributable to hGH therapy [2,24,71,95]. Populations with an increased baseline prevalence of scoliosis include children with Turner syndrome (TS), or Prader-Willi syndrome (PWS). Both of these populations have been studied for the impact of hGH on scoliosis. Bolar et al. found that in girls with TS treated with hGH, 44% had progression of scoliosis, and 69%

of those were considered non-serious progression [14]. The PWS study by Nagai et al., monitored scoliosis in 20 hGH-treated patients with PWS and observed progression in six, fluctuation in one, improvement in three, and no change in ten. There was no significant difference between the incidence of scoliosis in hGH-treated and untreated groups [63].

While there are reasons to think hGH therapy might benefit the bone disease in children with MPS, there is the possibility that they will not be able to respond to this therapy. Children with MPS may be resistant to hGH due to characteristic abnormalities of chondrocyte proliferation and accumulation of lysosomal storage material in the growth plate which have been documented in mice with MPS diseases [57,84]. In addition, it has been hypothesized that those children who are treated with HCT and irradiation may have local resistance to hGH due to damage of the growth plate by irradiation.

### 3.3. *Other potential benefits of hGH*

GH has been found to have other beneficial effects besides the impact on growth and bone. In patients who are GH deficient, a recent meta-analysis of 11 studies including 268 adult patients found that treatment with hGH improved exercise performance [99]. Treatment with hGH has also been shown to increase muscle mass and decrease fat mass in children who were born SGA, and those with PWS or TS, as well as increase pulmonary function in children with PWS [6,61,62,80,81, 100].

Various clinical trials of hGH have looked at the potential role of hGH in neuropsychological development/function. One study by Hokken-Koelega et al. found an improvement in performat and total IQ, problem behavior, and self perception in children who were SGA who were treated with hGH for 2–8 years [42]. Myers et al. reported an improvement in both language and cognitive functioning in children with PWS who were treated with hGH for 1 year compared to untreated children with PWS [62]. In addition, Arwert et al. studied patients with childhood onset hGH deficiency and found an improvement in both long-term and working memory after 6 months of treatment with hGH [7]. In contrast to the findings by Rovet et al. [77] and the above studies, Ross et al. did not find any difference in neurocognitive functioning in girls with Turner syndrome who were treated with hGH compared to those who were not [76]. Children with 18q deletion syndrome, a syndrome with significant developmental de-

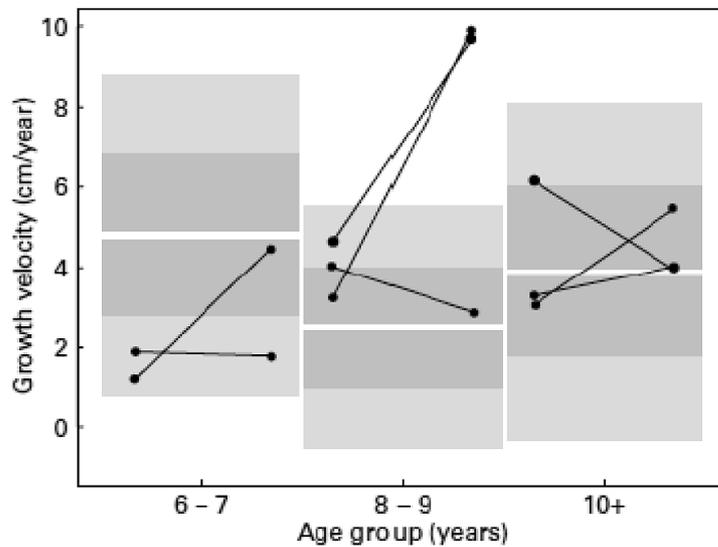


Fig. 5. Growth velocity before and after 1 year of treatment with GH for eight children with MPS IH. Each child is represented by a pair of connected points: the left point is growth velocity before treatment with GH and the right point is growth velocity 1 year later. The size of the point is proportional to the dose of GH (ranging from 0.26 to 0.45 mg/kg/week). The eight children are shown, within their age group (6–7 years, 8–9 years, 10 years and older) against reference levels for growth velocity mean (white horizontal lines) and 2 s.d. (gray rectangles) calculated from 48 children with MPS IH after HCT not treated with GH. GH=growth hormone; MPS IH=mucopolysaccharidosis type IH. (From Polgreen et al. Short-term growth hormone treatment in children with Hurler syndrome after hematopoietic cell transplantation. *BMT*. 2009; Mar 2: Epub ahead of print, with permission.)

lays, were found to have an improvement in nonverbal IQ after an average of 37 months of treatment with hGH [21]. The extent of the impact of hGH on neuropsychological functioning is yet to be fully defined, as some studies have also found no impact of hGH in these areas [75].

### 3.3.1. MPS I

There is currently one published study on the use of hGH in children with any MPS disease [70]. In this study, we described a retrospective review of hGH treatment in 8 children with MPS IH after HCT. The objectives of the study were to begin to examine (1) whether hGH treatment improved growth velocity in 8 children with MPS IH, and (2) the impact of hGH on skeletal abnormalities in these children.

Baseline growth velocity was  $3.5 \pm 1.5$  cm/yr ( $-2.6 \pm 1.9$  SDS) and increased to  $5.2 \pm 3.0$  cm/yr ( $-0.1 \pm 3.6$  SDS) after 1 year of treatment. Growth velocities before and after 1 year of treatment with hGH are shown in comparison to the mean (SD) growth velocity in age-matched children with MPS IH after HCT not treated with hGH in Fig. 5.

To explore the impact of total body irradiation (TBI) on growth, we compared children treated with hGH to historical controls matched for age and TBI status.

A history of TBI was associated with lower mean increases in growth velocity, by about the same amount in both treated and untreated children. hGH treatment increased growth velocity on average regardless of TBI status.

In addition to the growth response, we also examined the skeletal impact of treatment with hGH in these children and found one child developed slipped capital femoral epiphysis (SCFE) approximately 6 months after orthopedic surgery on the same femur which resulted in discontinuation of hGH treatment. This is a known complication of hGH; however the orthopedic manipulation may have increased her risk for this complication, as well as her history of TBI. Of 6 patients with radiographic data there was 1 progression of scoliosis, 1 progression of kyphosis, and 1 progression of genu valgum. No patient discontinued treatment due to progression of skeletal disease.

### 3.3.2. MPS II

There are no published data on the safety or efficacy of hGH in children with MPS II. The following is the experience of our clinical practice with hGH treatment in two boys with MPS II. Both boys were started on a low dose of hGH, due to the unknown change in risk for intracranial hypertension with hGH treatment, with

the intent of slowly increasing the dose to obtain full growth benefit.

Patient one is an 8 year old boy who was started on ERT at 5 years of age. Poor growth and a low IGF-1 prompted growth hormone stimulation testing for GH deficiency when he was 7 years old. The peak GH by arginine-clonidine stimulation testing previously described [69] was  $6.6 \mu\text{g/L}$  which is an insufficient response and diagnostic of GHD [22]. Due to the unknown risk in intracranial hypertension in children with MPS II treated with hGH, a lower than standard dose of hGH was started ( $0.1 \text{ mg/kg/wk}$ ). Growth velocity prior to initiation of treatment was  $2.7 \text{ cm/yr}$ , increased to  $10.3 \text{ cm/yr}$  after 6 months, and then decreased to  $3.4 \text{ cm/yr}$  after 12 months. Bone age (BA) was 4 years at chronologic age (CA) 7 years 8 months and 4 years 6 months when he was 8 years 3 months indicating a delayed bone age with normal bone age advancement during treatment with hGH. The IGF-1 level improved with treatment, but remained low suggesting insufficient hGH dose. He had no adverse effects of hGH during 1 year of treatment.

Patient two is a 4 year old boy who was started on ERT at 18 months of age. Poor growth and low IGF-1 prompted screening for GHD when he was 3 years old. Arginine-clonidine stimulation testing revealed a borderline response ( $9.6 \mu\text{g/L}$ ). Given the poor growth (growth velocity  $0 \text{ cm/yr}$ ) and borderline response to stimulation testing, hGH was started at  $0.1 \text{ mg/kg/wk}$ . Growth velocity after 3 months of treatment had increased to  $14.2 \text{ cm/yr}$ , and after 6 months was  $7.6 \text{ cm/yr}$ . Bone age was 3 years at chronologic age 3 years 9 months, and 3 year 6 months at chronologic age 4 years 3 months. This is a normal bone age and normal advancement of bone age during treatment with hGH. IGF-1 improved with treatment, but remained low, once again suggesting insufficient dosing of hGH. He had no adverse effects of hGH during 6 months of treatment except for some moderate pain in the knees and lower legs.

### 3.3.3. MPS IV

There are no published data on the safety or efficacy of hGH in children with MPS IV. The following is the experience of our clinical practice with hGH treatment in two girls with MPS IV.

Patient one is a 17 year 6 month old female who was referred for poor growth and delayed puberty. Baseline growth velocity was  $0.3 \text{ cm/yr}$  at 15 years 6 months. IGF-1 level was very low, however stimulated GH level was normal at  $22.6 \mu\text{g/L}$ . She was started on hGH

at a dose of  $0.3 \text{ mg/kg/wk}$ . After 12 months of treatment, growth velocity increased to  $2.7 \text{ cm/yr}$ , and in year two of treatment growth velocity was  $1.9 \text{ cm/yr}$ . Her bone age was 7 months 10 months at chronologic age 15 years 6 months and then 13 years at chronologic age 17 years 4 months after 6 months of estrogen replacement therapy. Estrogen replacement was initiated in year two of hGH treatment for treatment of delayed puberty. She experienced no adverse side effects, including no significant progression of kyphoscoliosis. Bone mineral density (BMD) was evaluated by DXA at the end of year 1 and year 2 of hGH treatment. In this period of time, BMD increased by 13.6% and 5.7% for lumbar spine and total body respectively. BMD Z-score adjusted by height age increased from  $-2.2$  to  $-1.2$  for lumbar spine and from  $-0.3$  to  $+0.9$  for total body. Initiation of estrogen replacement likely accounts for some of this improvement, in addition to treatment with hGH.

Patient two is a 13 year old female also referred for poor growth and delayed puberty. Baseline growth velocity was  $0 \text{ cm/yr}$  at the age of 11 years. IGF-1 was also very low, and her peak stimulated GH level was normal ( $11 \mu\text{g/L}$ ). She was started on hGH at  $0.3 \text{ mg/kg/wk}$ . hGH dose was increase to  $0.36 \text{ mg/kg/wk}$  after months of treatment and then continued at this dose. After 12 months of treatment growth velocity increased to  $4.7 \text{ cm/yr}$ , and in year 2 of treatment growth velocity was  $2.3 \text{ cm/yr}$ . Estrogen replacement was started after 2 years of treatment with hGH. Her bone age was 6 years 10 months at 11 years 11 months and 6 years 10 months at chronologic age 13 years 9 months. She experienced no adverse side effects, including no significant progression of kyphoscoliosis. BMD increased by 9.8% for lumbar spine and 4% for total body during year 2; Z-score adjusted by height age increased from  $-1.7$  to  $-1.1$  for lumbar spine and from  $+0.2$  to  $+0.7$  for total body.

### 3.3.4. MPS VI

One patient with MPS VI was treated with hGH in our practice. He was treated with ERT since the age of 7 years. This patient was started on hGH at the age of 12 years for short stature and decreased growth velocity. He was prepubertal by examination at that time. Growth hormone stimulation testing was normal. Baseline growth velocity was  $2.3 \text{ cm/yr}$ . Bone age was 9 years at 11 years 10 months. He was started on hGH at  $0.4 \text{ mg/kg/wk}$ ; this dose was increased to  $0.65 \text{ mg/kg/wk}$  over 3 years of treatment. At the end of year 1 growth velocity was  $5.9 \text{ cm/yr}$  (Tanner stage was

II); end of year 2 was 4 cm/yr (Tanner stage was III); and end of year 3 was 4.1 cm/yr (Tanner stage was IV). Bone age advancement was somewhat rapid with the bone age advancing 4 years over 3 years of treatment (BA 13 years at CA 14 years 10 months). Cervical spine stenosis was present and mildly progressive prior to hGH treatment. There was no significant progression by brain MRI during the 3 years of treatment; however the patient has had progression of clinical symptoms of cord compression including numbness and tingling in hands, and stable but persistent absence of sensory potentials and decreased median nerve compound potentials during EMG nerve conduction velocity testing after carpal tunnel release.

#### 4. Conclusions

This review of the current literature on growth and growth hormone in MPS revealed that short stature due to progressive growth failure is common in all MPS diseases. Weight and length are often normal at birth, but then growth failure results in short stature by 4–8 years of age in most children with MPS. Growth failure may be the presenting sign and therefore MPS should be considered in children evaluated for short stature.

ERT and HCT have been successful in prolonging the life expectancy of children with MPS. Although there appears to be an initial improvement in growth with these treatments, most children with MPS regardless of treatment have impaired growth. The etiology of this persistent, impaired growth is currently not well defined. It may be related to a lack of penetration of the enzyme into skeletal and connective tissues, persistent osteoblast or chondrocyte dysfunction, or resistance to growth hormone. Hormone deficiencies, particularly after HCT, likely contribute to the poor growth as well.

Although preliminary data suggests a benefit for some children with MPS from hGH, there are currently insufficient data on the safety and efficacy of hGH in children with MPS to recommend it as a standard of care. Controlled clinical trials are needed to determine if hGH will provide children with MPS the same benefits in growth, muscle strength, bone health, pulmonary function, and neuropsychological functioning that have been reported in other pediatric populations.

Further research is needed into the long term outcomes of both HCT and ERT. Questions remaining include: 1) Do children treated with cord blood HCT versus marrow HCT have better growth? 2) Now that

TBI is rarely used in the preparatory regimens of HCT, are growth outcomes better? 3) What is the long term growth pattern of children treated with ERT and the best protocol for administration of ERT? In addition, translational studies are needed to better understanding the etiology of growth failure in MPS which would help guide future therapeutic interventions.

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#### Conflicts of interest

Dr. Polgreen has research support from Genentech. Dr. Miller has research support from Genentech, Pfizer, Norditropin, and Tercica, and is part of the speaker's bureau for Genentech, Pfizer, and Norditropin. However, the work presented in this manuscript was not supported by any of these growth hormone companies.

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