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Short-term growth hormone treatment in children with Hurler syndrome after hematopoietic cell transplantation

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Summary

Children with Hurler syndrome experience progressive growth failure after hematopoietic cell transplantation (HCT). The goal of this study was to review the safety and efficacy of growth hormone (GH) in eight children with Hurler syndrome who were treated at our institution with GH for short stature or GH deficiency between 2005 and 2008. The age at initiation of treatment with GH was 9.6 ± 2.3 years and time since HCT was 7.5 ± 1.5 years. Mean GH dose was 0.32 mg/kg/week. Baseline growth velocity was 3.5 ± 1.5 cm/yr (−2.6 ± 1.9 SDS) and increased to 5.2 ± 3.0 cm/yr (−0.1 ± 3.6 SDS) after 1 year of treatment. 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. One patient discontinued GH due to slipped capital femoral epiphysis (SCFE). Preliminary data suggest that one year GH treatment may modestly improve growth velocity in children with Hurler syndrome.

Keywords

Growth hormone; insulin-like growth factor-1; short stature; mucopolysaccharidosis; Hurler; transplant

Introduction

Hurler syndrome, referred to as mucopolysaccharidosis type IH (MPS IH), is an autosomal recessive, lysosomal storage disease caused by a deficiency of alpha-L-iduronidase(1). This

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enzyme deficiency results in an accumulation of the glycosaminoglycans (GAGs) heparan and dermatan sulfate throughout the body, impacting multiple organ systems. Short stature is a common characteristic of MPS IH and is likely due to a combination of systemic, skeletal, and local growth plate abnormalities(2–5). MPS IH is characterized by cognitive and gross motor delays, coarse facial features, abnormal spinal curvatures (kyphosis, scoliosis), genu valgum, hernias, corneal clouding, enlarged tongue, hepatosplenomegaly and recurrent ear and nose infections; diagnosis is typically made before the age of 2 years (2, 6, 7).

Currently, most children with MPS IH are treated with hematopoietic cell transplantation (HCT)(8–10) and possibly enzyme replacement therapy (ERT) (11–13). The HCT conditioning regimens, which may include total body irradiation (TBI) and/or chemotherapy, often result in growth suppression, gonadal dysfunction, thyroid dysfunction, and epiphyseal growth plate damage, all potential causes of short stature (14–21). In addition, HCT conditioning regimens can cause GH deficiency, with the incidence of GH deficiency in non-MPS children post-HCT ranging from 11–84% depending on the specific preparatory regimen, GH testing method, and age at HCT (14–16, 18, 21, 22).

Although some of the metabolic dysfunction in MPS IH is corrected with HCT, short stature remains very common (81% at 8 years of age) and we have shown there is a progressive decrease in height SDS over time (3). In addition, the bone abnormalities may worsen over time, even after HCT (23–25). With current treatments, patients with MPS IH are expected to live into adulthood, and addressing severe short stature and bone abnormalities have become important issues for these patients. Although recombinant human GH is clinically being used to treat children with MPS IH who have short stature with or without GH deficiency, there are currently no reports in the literature of the efficacy or safety of GH in this population. Therefore, our objectives were to examine (1) whether GH treatment improved growth velocity in 8 children with MPS IH, and (2) the impact of GH on skeletal abnormalities in these children.

Methods

Subjects

We present data on 8 patients with MPS IH followed at the University of Minnesota for GH treatment of short stature and/or GH deficiency. These eight patients were identified by reviewing the medical records of 56 patients with MPS IH who survived at least one year after receiving HCT (marrow from an unrelated or related donor, or using an umbilical cord blood graft) at the University of Minnesota between September 1983 and April 2005. Historical control data was obtained from the remaining 48 children from this cohort of patients. Growth velocity was determined by height measurements a minimum of 12 months apart.

All patients treated with GH for a minimum of 6 months from this cohort were included. All HCT-related data were obtained from the University of Minnesota Pediatric Blood and Marrow Transplantation Database. The diagnosis of MPS IH was made on clinical grounds and confirmed by absent alpha-L-iduronidase activity. No patients received ERT either

before or after HCT. The transplant procedures and retrospective chart review were approved by the Institutional Review Board.

Analysis

Pretreatment growth velocity data were determined based on the measurement closest to a minimum of 12 months before initiation of GH treatment (range 17–29 months). Subsequent growth velocity during treatment was calculated over a minimum of 6 months. Skeletal films were reviewed by an orthopedic surgeon (J.D.S.), who determined a significant change to be ≥ 5 degrees of change in degree of spinal curvature or genu valgum. Two patients were not followed by an orthopedic surgeon at our institution and therefore did not have radiographs for review. Increase in growth velocity of ≥ 2 cm/yr was considered significant (a standard historically used in studies of response to GH)(26–28). Treatment data beyond 1 year were available for only 3 patients and thus were insufficient to analyze the effectiveness of GH treatment. These data were provided in case descriptions because of potential safety concerns with respect to skeletal deformities.

Endocrine evaluation

Endocrine evaluation at baseline and during GH treatment was done by a pediatric endocrinologist as previously described (3). Baseline endocrine evaluation was done within 1 year of starting GH for all patients except patient 6 for whom thyroid function was checked 1.4 years after starting GH and was normal. This included pubertal Tanner staging, and laboratory evaluation of thyroid function, and insulin-like growth factor-1 (IGF-1) levels as previously described (3), and GH stimulation testing with a dual agent protocol of arginine and clonidine, as described (29), at the discretion of the treating physician. IGF-1 SD scores were calculated based on reported references ranges or provided by the performing laboratory. Insulin-like growth factor binding protein-3 (IGFBP-3) levels were not measured for the majority of patients and thus were not included in the analyses. Height, weight, and growth velocity SD scores were calculated using GenenCALC™, version 3.0. A GH peak by stimulation testing less than 10 mcg/L was classified as GH deficiency(30).

Results

Response to GH treatment

Characteristics of HCT conditioning regimens, donor type, and post-engraftment enzyme activity are provided in Table 1. Age at initiation of GH was 9.6 ± 2.3 years (range 6 to 13.2 years). Body mass index (BMI) was 20.5 ± 3.4 kg/m^2 (range 15.9 to 24.3 kg/m^2) at baseline and remained in the normal range throughout treatment. Three children were pubertal at the time of initiation of GH, and 2 children started puberty during the course of treatment with GH. Growth velocities before and after 1 year of treatment with GH are shown in comparison to the mean (SD) growth velocity in age-matched children with MPS IH after HCT not treated with GH in figure 1.

Baseline growth velocity in GH treated children was 3.5 ± 1.5 cm/yr (−2.6 ± 1.9 SDS; range 1.2 to 6.1 cm/yr), and increased to 5.2 ± 3.0 cm/yr (−0.1 ± 3.6 SDS; range 1.8 to 9.8 cm/yr) after 1 year of treatment. Growth velocity increased by ≥ 2 cm/yr in 4 patients (50%).

Baseline height SDS was −3.9 ± 1.6 SDS (range −6.2 to −1.3 SDS). Height SDS remained stable after 1 year −3.7 ± 2.0 SDS (range −6.1 to −0.3 SDS). There was a gain in height of 2.9 to 12.5 cm. IGF-1 SDS also increased from −0.9 ± 2.4 to 2.8 ± 2.4 SDS (n = 6) over 1 year of treatment. No intracranial hypertension (pseudotumor cerebri) or hyperglycemia was reported.

Three patients had documented GH deficiency and would therefore be expected to have a better response to treatment with GH. Of the patients with GH deficiency 67% (n=3) responded with an increase in growth velocity ≥ 2 cm/yr compared to 50% (n=2) in the GH sufficient group. To explore the impact of TBI on growth, we compared children treated with GH to historical controls matched for age and TBI status. Weighted mean changes in growth velocity for the 4 subgroups of GH treated or untreated controls according to TBI status are shown in Figure 2; the means for the control subgroups were weighted to match the age distribution in the GH treated subgroups, where a treated child had multiple age-matched controls. Effects of TBI and GH appear additive. A history of TBI was associated with lower mean increases in growth velocity, by about the same amount in both treated and untreated children. GH treatment increased growth velocity on average regardless of TBI status (Figure 2).

Orthopedic Complications of MPS 1H

Radiographic data on scoliosis were available in 5 patients: 1 patient had progression of scoliosis and 4 remained stable. In regards to kyphosis, data were available on 3 patients: 1 patient had progression of kyphosis immediately adjacent to previous fusion of the thoracic spine from T1-T8, 1 improved, and the other one remained stable. Genu valgum data were available on 3 patients: genu valgum in 1 patient worsened in both legs, 1 patient had improvement in the left genu valgum and the right was stable, and the third patient had no significant change (Table 2). One patient discontinued GH due to slipped capital femoral epiphysis (SCFE), which is not a typical skeletal manifestation of Hurler syndrome. No patients discontinued GH due to worsening scoliosis, kyphosis, or genu valgum.

Patient specific data

All patients had normal alpha-L-iduronidase levels (>60%) throughout GH treatment, except patient 7 whose alpha-L-iduronidase level ranged from 30– 50% during treatment with GH. Treatment with GH was not discontinued, and thyroid function and puberty were normal, unless specified below:

Patient 1 had bilateral carpal tunnel release, bilateral epiphyseal stapling, bilateral femoral and iliac osteotomies before GH was started. GH was stopped due to financial limitations.

Patient 2 had a history of bilateral epiphyseal stapling, hip osteotomies, and innominate osteotomies. During GH therapy he had posterior C1-C2 spinal fusion for instability with a history of C1-C2 stenosis present since before initiation of GH. He has continued on GH for 2.8 years (Fig. 1). At last evaluation, growth velocity had increased from 1.8 cm/yr (−4.8 SDS) to 4.5 cm/yr (−0.9 SDS), and height increased from 100 cm (−6.1 SDS) to 105 cm (−5.7 SDS) over 1.1 years.

Patient 3 had a history of multiple orthopedic surgeries: bilateral carpal tunnel and trigger release, bilateral proximal tibial epiphyseal stapling, bilateral varus femoral osteotomy, removal of left knee staples, spinal fusion of T9-L3, and removal of bilateral hip and knee hardware, all before initiation of GH therapy. She was diagnosed with precocious puberty at age 8 years 7 months, based on parental report of pubertal signs a few months before the age of 8 years, and started on Lupron therapy and GH for the treatment of short stature. She has continued on GH for 2.4 years (Fig. 1). At last evaluation, growth velocity and height SDS had remained stable at 3.0 cm/yr (−3.8 SDS) and −2.8 SDS respectively.

Patient 4 had no prior orthopedic surgeries. After 1 year 6 months of treatment, GH was discontinued as a precaution due to her sister's development of slipped capital femoral epiphysis (SCFE) while on GH treatment.

Patient 5 had a history of anteroposterior spinal fusion of T10-L2 before initiation of GH treatment.

Patient 6 underwent posterior spinal fusion at 5 years of age, and then elective bilateral proximal and distal tibial hemi-epiphysiodesis, for bilateral genu valgum and hip dysplasia, 1 year 10 months after GH treatment initiation. He has continued on GH for 3.0 years (Fig. 1). At last evaluation, growth velocity had decreased from 5.4 cm/yr (0.2 SDS) to 4.3 cm/yr (−2.6 SDS), and height SDS remained stable: −5.9 SDS to −5.7 SDS.

Patient 7 had bilateral epiphyseal stapling, bilateral carpal tunnel and trigger finger release, bilateral varus osteotomy, and spinal fusion from T11 to L3 before GH treatment.

Patient 8 discontinued GH treatment due to slipped capital femoral epiphysis (SCFE) which occurred 6 months after bilateral distal femoral hemiepiphysiodesis and bilateral femoral implant removal. She had a history of bilateral carpal tunnel release, posterior spinal fusion of T7-L3, anterior spinal fusion, bilateral varus osteotomies, right proximal medial tibial epiphyseal stapling, and removal of knee staples prior to GH therapy. She was pubertal at the time of initiation of GH treatment, however had developed gonadal failure. Estrogen therapy was not started until after GH had been discontinued.

Discussion

To our knowledge, this is the first paper to report the impact of treatment of short stature with GH in children with MPS IH. Our data suggest that children with MPS IH after HCT may respond to a short-term treatment with GH. While some children experienced limited progression of abnormal spinal curvatures or genu valgum, a causal relationship to GH treatment is difficult to determine due to the unknown natural progression of skeletal deformities in MPS IH over time.

A clinically appropriate assessment of a "response to treatment" is difficult in children with MPS IH where (1) baseline growth velocity is often very low and thus a smaller increase in growth velocity may be more significant than for other patient populations without MPS IH,

(2) skeletal abnormalities make accurate height measurements difficult, and (3) the natural progression of growth and skeletal disease is currently not entirely defined. If a response to treatment with GH is defined as ≥ 2 cm/yr (a standard historically used in studies of response to GH), then 50% of the patients responded after 1 year of treatment. This improvement in height velocity resulted in an increase in height SDS of ≥ 0.25 SDS (31) in 50% of patients after 1 year of treatment. It is important to note, however, that children with MPS IH after HCT without treatment with GH experience progressive decrease in height SDS over time (3). Thus, no significant decrease in height SDS may actually be consistent with an improvement in growth compared to what would have been expected for these children.

A potential adverse side effect of treatment with GH is worsening of the orthopedic complications characteristic of MPS IH. Genu valgum, scoliosis, and kyphosis are very common in children with MPS IH even after HCT. In our reference cohort (3), 60% of the children had a history of orthopedic surgery: 54% had genu valgum surgery, 33% had spinal surgery. In the group treated with GH, 75% had a history of genu valgum surgery and 88% a history of spinal surgery. Although it is generally thought that any growth has the potential to worsen scoliosis, there is no clear conclusion in the literature regarding the impact of GH treatment on the prevalence or progression of scoliosis or kyphosis. While some researchers have found a higher than expected percentage and rate of curve progression (32), others have observed little to no progression attributable to GH therapy (33–35). Populations with an increased baseline prevalence of scoliosis, similar to MPS IH, include children with Turner syndrome, or Prader-Willi syndrome. Both of these populations have been studied for the impact of GH on scoliosis. *Bolar et al* found that in girls with Turner syndrome treated with GH, 44% had progression of scoliosis, and 69% were considered non-serious progression (36). *Nagai et al.* monitored scoliosis in 20 GH-treated patients with Prader-Willi syndrome 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 GH-treated and untreated groups (37). In our study, we observed progression of scoliosis in one patient, progression of kyphosis in one patient (which did not occur until year 2 of treatment), and improvement of kyphosis in one. In 3 patients with lower extremity radiographs, we observed progression of genu valgum in one patient (which did not result in discontinuation of treatment), and improvement (secondary to stapling) in one patient. Finally, although sub-normal alpha-L-iduronidase levels post transplant have been associated with an increased risk of carpal tunnel syndrome, (25), another commonly observed orthopedic problem in this population, the one patient with low enzyme activity in our study did not develop an orthopedic complication while on GH.

Previous studies have provided data indicating a higher incidence of SCFE in patients receiving GH therapy (34, 36, 38–40). Risk factors for the development of SCFE include obesity, prior radiation therapy, GH deficiency and growth during puberty (38–42). Blethen and Rundle, analyzing data from the National Cooperative Growth Study (NCGS), found that children who developed SCFE were more likely to have grown more slowly during the first year of treatment with GH compared to those who did not develop SCFE (39). Of the eight children in our study, one developed SCFE (patient 8), leading to termination of GH

therapy. Her BMI was normal for age and gender (22.1 kg/m2, +1.1 SD). However she had multiple risk factors for the development of SCFE: she was the oldest patient at initiation of GH therapy, the furthest progressed in pubertal development, she demonstrated a decrease in growth velocity following initiation of GH treatment, and had received TBI prior to HCT. Finally, SCFE occurred only 6 months following bilateral femoral orthopedic surgeries which may also have contributed to this adverse event.

Single dose, versus fractionated, TBI has been associated with an attenuated response to GH (22, 43) possibly due to local damage at the growth plate. Six of eight patients in our study received TBI with their conditioning regimens (5 received single dose TBI), which may have resulted in some local growth plate resistance to GH. By comparing our group to age and TBI matched untreated controls, we found a trend towards improved growth in children treated with GH whether or not they had received TBI. However those with no history of TBI treated with GH had the largest increase in mean growth velocity.

Continued deposition of GAG may exacerbate local resistance to GH as well. It has been reported that the skeletal abnormalities characteristic of MPS IH persist and may even worsen in time after HCT (23–25), suggesting insufficient penetrance of alpha-L-iduronidase enzyme into the boney architecture and a continued accumulation of GAG at the growth plates after HCT. This may have contributed to the fact that the one patient in this study with low alpha-L-iduronidase levels did not respond to treatment with GH. If there is indeed local growth plate resistance to GH, then higher doses of GH may be necessary to achieve a significant growth response in children with MPS IH after HCT. This may be limited however, by the significant elevations in IGF-1 levels we found in our patients treated with GH, although no accompanying IGFBP-3 levels were measured.

The limitations of this study are the retrospective nature and small sample size due to the rarity of this disease. The small sample size makes statistical analysis of differences between groups meaningless. A larger sample size could help predict who may benefit from treatment and who may not. In addition, the multiple factors that may impact growth velocity, e.g. pubertal stage, orthopedic abnormalities, TBI, and age, make it difficult to make definitive conclusions in such a small sample. While puberty may have contributed to an increase in growth velocity, the increase in IGF-1 SDS values, which are adjusted for age, would argue in favor of a GH effect. Finally, the HCT preparative regimens have changed since the patients in this study received their transplants. Most institutions including our own, are using chemotherapy based regimens such as targeted busulfan and cyclophosphamide, and are not using TBI prior to transplantation. This may ultimately affect the risk of GH deficiency, and could perhaps alter the response to therapy as discussed above.

Conclusions

Our observations suggest a potential, albeit modest, increase in growth velocity in children with MPS IH after 1 year of treatment with GH. Children without a history of TBI may respond better to treatment with GH than those who have been treated with TBI. We conclude that orthopedic co-morbidities need to be followed closely by orthopedic physicians who are familiar with MPS diseases, but do not necessarily exclude patients from

receiving a trial of GH. Finally, due to the occurrence of SCFE in one patient, it would be prudent to avoid GH treatment during and within a year after orthopedic procedures involving the femur.

More data are needed on the long-term height and safety outcomes of treatment with GH in this population, and in particular on the impact of GH treatment on the characteristic skeletal abnormalities and orthopedic outcomes. Since progression of skeletal deformities may contribute to reduction in height, other measurements of spinal and longitudinal bone growth will need to be applied in future studies to assess response to GH.

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References

1. Bach G, Friedman R, Weissmann B, Neufeld EF. The defect in the Hurler and Scheie syndromes: deficiency of -L-iduronidase. Proc Natl Acad Sci U S A. 1972; 69(8):2048–51. [PubMed: 4262258]
2. Neufeld, E.; Munezer, I. The Metabolic & Molecular Basis of Inherited Disease. 8. McGraw-Hill; New York: 2001. p. 3421-3452.
3. Polgreen L, Plog M, Tolar J, Himes JH, Orchard P, Whitley C, et al. Growth and endocrine function in patients with Hurler syndrome after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2008; 41(12):1005–1011. [PubMed: 18278070]
4. Russell C, Hendson G, Jevon G, Matlock T, Yu J, Aklujkar M, et al. Murine MPS I: insights into the pathogenesis of Hurler syndrome. Clin Genet. 1998; 53(5):349–61. [PubMed: 9660052]
5. Silveri CP, Kaplan FS, Fallon MD, Bayever E, August CS. Hurler syndrome with special reference to histologic abnormalities of the growth plate. Clin Orthop Relat Res. 1991; (269):305–11. [PubMed: 1907534]
6. Dusing SC, Thorpe D, Rosenberg A, Mercer V, Escolar ML. Gross motor abilities in children with Hurler syndrome. Dev Med Child Neurol. 2006; 48(11):927–30. [PubMed: 17044963]
7. Ashworth JL, Biswas S, Wraith E, Lloyd IC. The ocular features of the mucopolysaccharidoses. Eye. 2006; 20(5):553–63. [PubMed: 15905869]
8. Krivit W. Allogeneic stem cell transplantation for the treatment of lysosomal and peroxisomal metabolic diseases. Springer Semin Immunopathol. 2004; 26(1–2):119–32. [PubMed: 15452666]
9. Staba SL, Escolar ML, Poe M, Kim Y, Martin PL, Szabolcs P, et al. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. N Engl J Med. 2004; 350(19):1960–9. [PubMed: 15128896]
10. Vellodi A, Young EP, Cooper A, Wraith JE, Winchester B, Meaney C, et al. Bone marrow transplantation for mucopolysaccharidosis type I: experience of two British centres. Arch Dis Child. 1997; 76(2):92–9. [PubMed: 9068295]
11. Tolar J, Grewal SS, Bjoraker KJ, Whitley CB, Shapiro EG, Charnas L, et al. Combination of enzyme replacement and hematopoietic stem cell transplantation as therapy for Hurler syndrome. Bone Marrow Transplant. 2008; 41(6):531–5. [PubMed: 18037941]
12. Cox-Brinkman J, Boelens JJ, Wraith JE, O'Meara A, Veys P, Wijburg FA, et al. Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. Bone Marrow Transplant. 2006; 38(1):17–21. [PubMed: 16715104]

13. Grewal SS, Wynn R, Abdenur JE, Burton BK, Gharib M, Haase C, et al. Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. Genet Med. 2005; 7(2):143–6. [PubMed: 15714083]
14. Frisk P, Arvidson J, Gustafsson J, Lonnerhölm G. Pubertal development and final height after autologous bone marrow transplantation for acute lymphoblastic leukemia. Bone Marrow Transplantation. 2004; 33:205–210. [PubMed: 14628079]
15. Shalitin S, Phillip M, Stein J, Goshen Y, Carmi D, Yaniv I. Endocrine dysfunction and parameters of the metabolic syndrome after bone marrow transplantation during childhood and adolescence. Bone Marrow Transplant. 2006
16. Perkins JL, Kunin-Batson AS, Youngren NM, Ness KK, Ulrich KJ, Hansen MJ, et al. Long-term follow-up of children who underwent hematopoeitic cell transplant (HCT) for AML or ALL at less than 3 years of age. Pediatr Blood Cancer. 2007
17. Bakker B, Massa GG, Oostdijk W, Van Weel-Sipman MH, Vossen JM, Wit JM. Pubertal development and growth after total-body irradiation and bone marrow transplantation for haematological malignancies. Eur J Pediatr. 2000; 159(1–2):31–7. [PubMed: 10653326]
18. Couto-Silva AC, Trivin C, Esperou H, Michon J, Baruchel A, Lemaire P, et al. Final height and gonad function after total body irradiation during childhood. Bone Marrow Transplant. 2006; 38(6):427–32. [PubMed: 16878146]
19. Legault L, Bonny Y. Endocrine complications of bone marrow transplantation in children. Pediatr Transplant. 1999; 3(1):60–6. [PubMed: 10359033]
20. Shankar SM, Bunin NJ, Moshang T Jr. Growth in children undergoing bone marrow transplantation after busulfan and cyclophosphamide conditioning. J Pediatr Hematol Oncol. 1996; 18(4):362–6. [PubMed: 8888742]
21. Bakker B, Oostdijk W, Bresters D, Walenkamp MJ, Vossen JM, Wit JM. Disturbances of growth and endocrine function after busulphan-based conditioning for haematopoietic stem cell transplantation during infancy and childhood. Bone Marrow Transplant. 2004; 33(10):1049–56. [PubMed: 15048143]
22. Huma Z, Boulad F, Black P, Heller G, Sklar C. Growth in children after bone marrow transplantation for acute leukemia. Blood. 1995; 86(2):819–24. [PubMed: 7606013]
23. Weisstein JS, Delgado E, Steinbach LS, Hart K, Packman S. Musculoskeletal manifestations of Hurler syndrome: long-term follow-up after bone marrow transplantation. J Pediatr Orthop. 2004; 24(1):97–101. [PubMed: 14676543]
24. Field RE, Buchanan JA, Copplemans MG, Aichroth PM. Bone-marrow transplantation in Hurler's syndrome. Effect on skeletal development. J Bone Joint Surg Br. 1994; 76(6):975–81. [PubMed: 7983131]
25. Khanna G, Van Heest AE, Agel J, Bjoraker K, Grewal S, Abel S, et al. Analysis of factors affecting development of carpal tunnel syndrome in patients with Hurler syndrome after hematopoietic cell transplantation. Bone Marrow Transplant. 2007; 39(6):331–4. [PubMed: 17277793]
26. Cave CB, Bryant J, Milne R. Recombinant growth hormone in children and adolescents with Turner syndrome. Cochrane Database Syst Rev. 2003; (3):CD003887. [PubMed: 12917993]
27. Lanes R, Carrillo E. Long-term therapy with a single daily subcutaneous dose of growth hormone releasing hormone (1–29) in prepubertal growth hormone deficient children. Venezuelan Collaborative Study Group. J Pediatr Endocrinol. 1994; 7(4):303–8. [PubMed: 7735367]
28. Rosenbloom AL, Knuth C, Shulman D. Growth hormone by daily injection in patients previously treated for growth hormone deficiency. South Med J. 1990; 83(6):653–5. [PubMed: 2192462]
29. Polgreen L, Steiner M, Dietz CA, Manivel JC, Petryk A. Thymic hyperplasia in a child treated with growth hormone. Growth Horm IGF Res. 2007; 17(1):41–6. [PubMed: 17141546]
30. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab. 2000; 85(11):3990–3. [PubMed: 11095419]
31. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr. 2003; 143(4):415–21. [PubMed: 14571209]

32. Wang E, Drummond D, Dormans J, Moshang T, Davidson R, Gruccio D. Scoliosis in patients treated with growth hormone. J Pediatr Orthop. 1997; 17(6):708–711. [PubMed: 9591970]
33. Day G, McPhee I, Batch J, Tomlinson F. Growth rates and the prevalence and progression of scoliosis in short-statured children on Australian growth hormone treatment programmes. Scoliosis. 2007; 2(3)
34. Quigley C, Gill A, Crowe B, Robling K, Chipman J, Rose S, et al. Safety of Growth Hormone Treatment in Pediatric Patients with Idiopathic Short Stature. J Clin Endocrinol Metab. 2005; 90(9):5188–5196. [PubMed: 15899952]
35. Vidil A, Journeau P, Soulie A, Padovani J, Pouliquen J. Evolution of Scoliosis in Six Children Treated wtih Growth Hormone. J Pediatr Orthopaedics Part B. 2001; 10:197–200.
36. Bolar K, Hoffman AR, Maneatis T, Lippe B. Long-Term Safety of Recombinant Human Growth Hormone in Turner Syndrome. J Clin Endocrinol Metab. 2007 jc.2007–1723.
37. Nagai T, Obata K, Obata T, Murakami N, Katada Y, Yoshino A, et al. Growth Hormone Therapy and Scoliosis in Patients with Prader-Willi Syndrome. American Journal of Medical Genetics Part A. 2006; 140A:1623–1627. [PubMed: 16770808]
38. Nishi Y, Tanaka T, Fujieda K, Hanew K, Hirano T, Igarashi Y, et al. Slipped Capital Femoral Epiphysis, Perthes' Disease and Scoliosis in Children with Growth Hormone Deficiency. Endocrine Journal. 1998; 45(Suppl):S167–169. [PubMed: 9790256]
39. Blethen SL, Rundle AC. Slipped Capital Femoral Epiphysis in Children Treated with Growth Hormone. Horm Res. 1996; 46:113–116. [PubMed: 8894665]
40. Maneatis T, Baptista J, Connelly K, Blethen S. Growth Hormone Safety Update from the National Cooperative Growth Study. J Pediatr Endocrin Metab. 2000; 13:1035–1044.
41. Rappaport E, Fife D. Slipped capital femoral epiphysis in growth-hormone deficient patients. Am J Dis Child. 1985; 139:396–399. [PubMed: 3976631]
42. Exner G. Growth and pubertal development in slipped capital femoral epiphysis: a longitudinal study. J Pediatr Orthop. 1986; 6:403–409. [PubMed: 3734062]
43. Giorgiani G, Bozzola M, Locatelli F, Picco P, Zecca M, Cisternino M, et al. Role of busulfan and total body irradiation on growth of prepubertal children receiving bone marrow transplantation and results of treatment with recombinant human growth hormone. Blood. 1995; 86(2):825–31. [PubMed: 7606014]

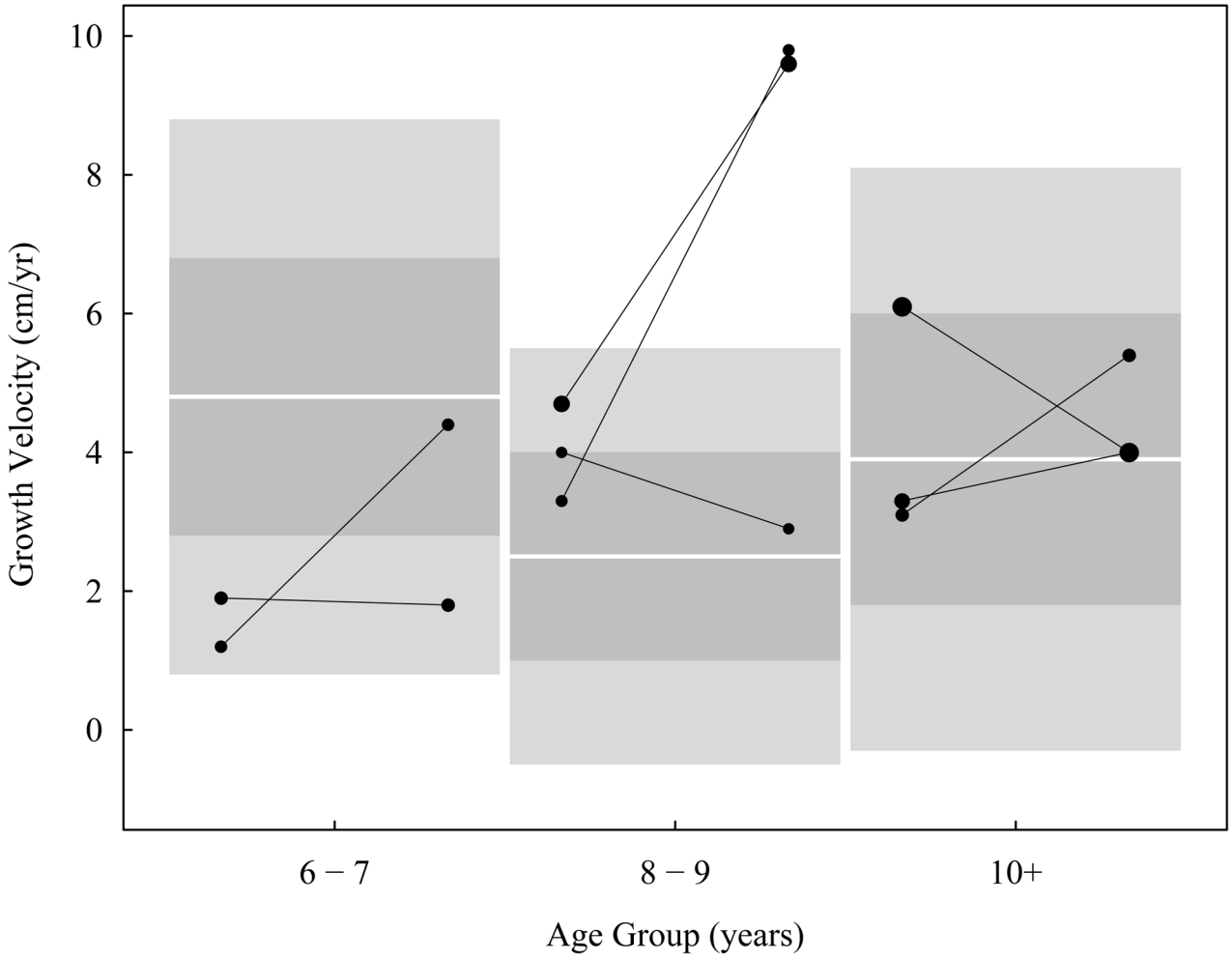

Figure 1. Growth velocity before and after 1 year of treatment with GH for 8 children with MPS IH

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 one year later. The size of the point is proportional to the dose of GH (ranging from 0.26 to 0.45 mg/kg/wk). The 8 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 standard deviations (gray rectangles) calculated from 48 children with MPS IH after HCT not treated with GH.

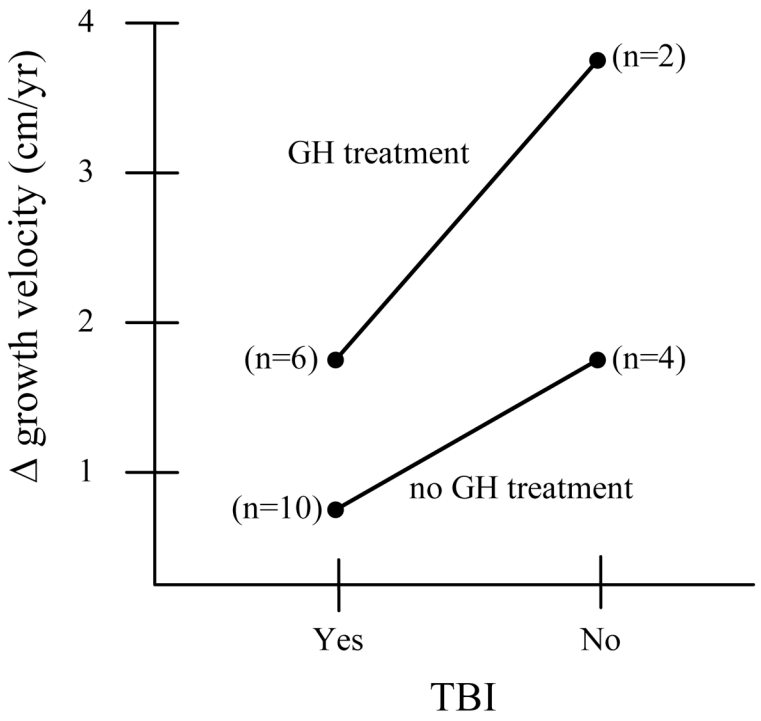

Figure 2. Effects of growth hormone and TBI on change (Δ) in growth velocity over 1 year
GH treated group is matched by age and TBI status with historic, non-GH treated, controls.

Table 1

HCT characteristics of 8 children with MPS IH treated with GH

Patient	Gender	Age at HCT (yrs)	Conditioning regimen	donor type	enzyme activity
1	male	1.1	Bu 320 mg/m^2	unrelated	normal
			Cy 120 mg/kg ATG 60 mg/kg TBI 750 cGy		
2	male	1.1	Bu 320 mg/m^2	related	normal
			Cy 120 mg/kg ATG 60 mg/kg TBI 750 cGy		
3	female	1.1	Cy 120mg/kg	unrelated	normal
			ATG 60mg/kg TBI 1400 cGy (7 fractions)		
		1.5*	Bu 20mg/kg Cy 200 mg/kg ATG 60mg/kg	unrelated	
4	female	1.2	Bu 320 mg/m^2	Cord-URD	normal
			Cy 120 mg/kg ATG 120 mg/kg TBI 750 cGy		
5	female	1.8	Bu 20 mg/kg	Unrelated	normal
			Cy 200 mg/kg ATG 90 mg/kg		
6	male	1.9	Bu 320 mg/m^2	unrelated	normal
			Cy 120 mg/kg		

Patient	Gender	Age at HCT (yrs)	Conditioning regimen	donor type	enzyme activity
			ATG 60 mg/kg		
			TBI 750 cGy		
		2.6*	Bu 20 mg/kg	unrelated	
			Cy 200/kg		
			ATG 60 mg/kg		
7	male	1.4	Bu 20 mg/kg	unrelated	**low**
			Cy 200 mg/kg		
			ATG 60 mg/kg		
8	female	6.0	Bu 320 mg/m^2	Unrelated	normal
			Cy 120 mg/kg		
			ATG 60 mg/kg		
			TBI 750 cGy		

Bu = busulfan; Cy = cyclophosphamide; ATG = anti-thymocyte immunoglobulin; TBI = total body irradiation;

*second HCT, normal = >60%, low = 30–60%.

Table 2

Pre- and 1-year GH treatment data.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Gender	**Male**	**Male**	**Female**	**Female**	**Female**	**Male**	**Male**	**Female**
BASELINE								
age (years)	6.0	7.8	8.6	8.8	9.5	11.0	11.5	13.2
Pubertal stage	P1, T1	P1, T1	**P3, B1**	P1, B1	**P2, B1**	P1, T1	P1, T1	**P3, B5**
peak GH by stimulation test (μg/L)	NA	NA	25.3	**8.1**	**19**	**4.5**	NA	**1.8**
IGF-1, nmol/L (SD)	**4.7 (−2.6)**	**15.3 (−1.9)**	45.2 (3.7)	29.4 (0.8)	15.0 (−1.4)	NA	**16.1 (−2.3)**	**14.6 (−2.7)**
GH dose (mg/kg/week)	0.27	0.30	0.29	0.40	0.28	0.30	0.33	0.40
Growth velocity, cm/yr (SD)	**1.2 (−5.3)**	**1.9 (−4.6)**	**4.0 (−2.2)**	**4.7 (−1.3)**	**3.3 (−3.1)**	**3.1 (−2.8)**	**3.3 (−2.5)**	**6.1 (0.7)**
height, cm (SD)	91.1 (−4.8)	97 (−5.6)	117.1 (−2.5)	124 (−1.3)	115.6 (−3.1)	103.5 (−6.2)	117.6 (−4.2)	133.0 (−3.6)
weight, kg (SD)	13.2 (−4.2)	16.5 (−3.7)	32.7 (0.8)	29.27 (0.2)	32 (0.5)	18.8 (−4.8)	33.6 (−0.7)	39 (−1.0)
BMI	15.9	17.5	23.9	19	23.9	17.6	24.3	22.1
IDUA	normal	normal	normal	normal	normal	normal	low	normal
YEAR 1								
age (years)	6.8*	9.5	9.6	10.1*	10.3	11.8	12.5*	14.5*
Pubertal stage	P1, T1	P1, T1	**P4, B2**	**P2, B4**	**P2, B2**	P1, T1	**P3,TNR**	**P4, B5**
IGF-1, nmol/L (SD)	22.9 (1.9)	NA	80.4 (4.4)	121.3 (6.4)	51.1 (0.9)	32.3 (−0.3)	NA	93.3 (3.3)
GH dose (mg/kg/week)	0.29	0.30	0.23	0.33	0.25	0.30	0.36	0.50
Growth velocity, cm/yr (SD)	**4.4 (−1.8)**	**1.8 (−4.8)**	**2.9 (−3.6)**	**9.6 (4.6)**	**9.8 (4.5)**	**5.4 (0.2)**	**4.0 (−2.1)**	**4.0 (2.2)**
height, cm (SD)	94.6 (−5.0)	100 (−6.1)	120 (−2.6)	136.5 (−0.3)	123.4 (−2.5)	107.8 (−5.9)	121.6 (−4.2)	138.2 (−3.3)
weight, kg (SD)	14.4 (−4.1)	18.2 (−4.1)	31.1 (0)	40 (0.9)	36.7 (0.4)	18.9 (−5.3)	39.4 (4.2)	44.5 (−1.1)
BMI	16.1	18.2	21.6	21.5	24.1	16.3	26.7	23.3
Complications			**progression genu valgum**	**progression scoliosis**		**progression kyphosis**		**SCFE**

yr = year, ht = height, SDS = standard deviation score, GV = growth velocity; IDUA = alpha-L-iduronidase activity (nmol/mg protein/hr); NA = not available; SCFE = slipped capital femoral epiphysis; P = pubic hair Tanner stage; T = testes Tanner stage; B = breast Tanner stage.

*discontinued GH.