Is treatment with growth hormone effective in children with cerebral palsy?

Case report

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Children with cerebral palsy (CP) often have poor linear growth during childhood, resulting in a diminished final adult height. Here we report a female with CP and short stature but without growth hormone (GH) deficiency who exhibited increased growth during treatment with GH. We also report two other children with CP who were treated with GH: one female with a history of leukemia, and a male with Klinefelter syndrome. These two children were both found to be GH-deficient by insulin provocative GH testing and responded to treatment with increased growth rate. Growth improved to a greater extent in the two children with apparent GH deficiency. In summary, it is felt that GH therapy might be beneficial for children with CP and warrants further investigation.

There is a high incidence of short stature and growth failure in children with cerebral palsy (CP; Stevenson et al. 1994, Klauschie and Rose 1996, Krick et al. 1996). Krick et al. studied the growth patterns of 360 children with CP, and reported that on average they were 5% shorter at 2 years of age and more than 10% shorter at 8 years of age in comparison with their unaffected counterparts. Poor linear growth in CP has been attributed to nutritional factors as well as non-nutritional factors such as those involving the neurologic or endocrine systems (Stallings et al. 1993, Stevenson et al. 1995). Stevenson et al. reported growth parameters in 171 children with CP, attending an outpatient clinic in a tertiary-care setting, and found that in this population linear growth rate declined with age, independent of nutritional status. The growth hormone (GH) axis has not been systematically studied in children with CP but there have been reports of abnormalities in GH secretion in this population (Hayashi et al. 1989, Anderson and Lund 1995, Coniglio and Stevenson 1995, Coniglio et al. 1996).

In conditions of growth failure such as GH deficiency, Turner syndrome, Prader–Willi syndrome, and children born small for gestational age, treatment with human recombinant GH is effective in increasing linear growth rate and final height (de Zegher et al. 1996, Sas et al. 1999, Carrel et al. 2000, Saenger 2000). In addition, GH therapy has been shown to have beneficial effects on body composition (by increasing muscle mass and decreasing fat mass), strength, bone mineral density, and quality of life in certain populations.

This patient review was conducted under the guidelines of the Children's Hospital of Philadelphia and University of California Los Angeles Institutional Review Boards.

Case reports

PATIENT 1

Patient 1 was born at 29½ weeks' gestational age following a pregnancy that was complicated by a car accident. She required a 2-month hospitalization in the intensive care unit after birth. She had significant motor delay and spasticity and was diagnosed with spastic hemiplegia at 9 months of age. She presented to the endocrinologist at the age of 2 years 8 months with poor growth, at which time her height was 2.5 standard deviations (SDs) below the mean for her age (–2.5SDs). Functionally, she was fully ambulatory. Insulin provocative GH testing at the age of 3 years revealed a peak GH level of 16ng/ml, thus excluding the diagnosis of GH deficiency. Her growth rate remained abnormally low and at the age of 7½ years her height was –3.3SDs and she was started on daily injections of recombinant human GH at a dose of 0.04mg/kg per day. Her growth rate improved and after 2 years of treatment her height is –2.5SDs. She has had no side effects and her mother reports an increase in overall strength and energy since starting GH.

PATIENT 2

Patient 2, who was born preterm at 32 weeks and had spastic diplegia, was diagnosed with acute lymphocytic leukemia at 8 months of age, necessitating treatment including chemotherapy, radiotherapy, and an unmatched bone marrow transplant at the age of 2½ years. At 5 years of age, in remission, she presented with growth failure; an endocrinologic work-up revealed GH deficiency, identified by a subnormal GH response to insulin provocative testing (peak GH level 5ng/ml). At that time her height was –2.25SDs. Functionally, she was fully ambulatory. She was treated with recombinant depot GH at a dose of 1.5mg/kg per month. Her growth rate increased markedly, and 2 years into treatment her height had improved to –0.6SDs. She had no side effect from the therapy.

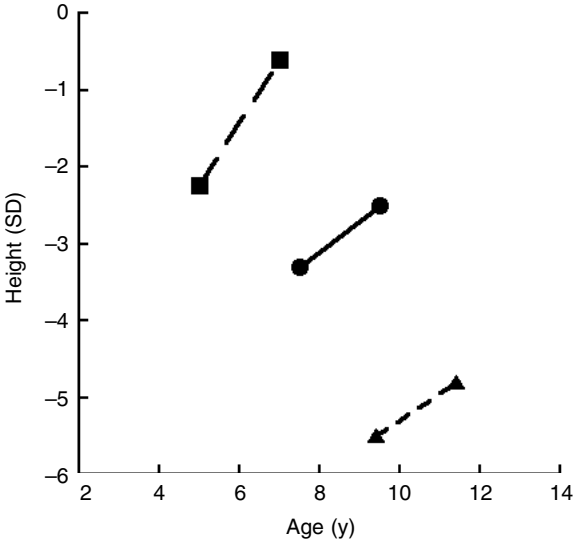

Figure 1: *Change in height score (SDs) after growth hormone therapy in children with cerebral palsy. All patients were measured with a Harpenden stadiometer (Holtain Ltd, Crymych, UK) while standing.* ●*, Patient 1;* ■*, Patient 2;* ▲*, Patient 3.*

PATIENT 3

Patient 3 is a male with severe spastic quadriplegia and Klinefelter syndrome. He presented to the endocrinologist at the age of 8 years 6 months for poor growth and extreme short stature, with a height score of –5.5SDs. He also displayed severe muscle wasting. He was diagnosed with GH deficiency when he failed an insulin provocative GH test with a peak GH level of 3.3ng/ml. At the age of 9 years 5 months he was started on daily treatment of recombinant human GH at a dose of 0.05mg/kg per day. His growth rate improved, and at 2 years into treatment his height had increased to –4.8SDs. Before the initiation of GH therapy, the patient required a wheelchair and displayed very limited mobility. During treatment with GH his physicians noted a marked increase in his strength, and within a year he was using a walker and performing tasks that he had previously been unable to carry out.

Discussion

GH treatment stimulates skeletal growth in pediatric patients with growth failure due to GH deficiency, chronic renal insufficiency, Turner syndrome, and Prader–Willi syndrome, and in children born small for gestational age (de Zegher et al. 1996, Sas et al. 1999, Carrel et al. 2000). In the three children presented here with CP and short stature who were treated with GH, linear growth rate increased significantly without side effects. Growth improved to a greater extent in the two children with apparent GH deficiency than in the child (Patient 1) with no apparent GH deficiency.

A better understanding of the causes and mechanisms of growth impairment in CP could lead to its prevention or treatment in some children. Although the GH axis has not been systematically studied in children with CP, there have been reports suggesting abnormal GH secretion in this population. Coniglio et al. (1996) studied 10 children with CP and short stature and found that six had abnormally low spontaneous GH secretion and subnormal GH release in response to pharmacological stimulation. In this study, linear growth rate was the single best clinical predictor of GH status. Hayashi et al. (1989) reported subnormal GH responses in four males with athetoid CP after administration of the GH clonidine, and in seven males with spastic CP after administration of GH-releasing hormone. Here we report on three children with CP and short stature, two of whom were found to have GH deficiency by insulin provocative GH testing. These children might have anatomical or neurochemical abnormalities of the hypothalamic–pituitary axis that are associated both with their CP and their apparent GH deficiency. The diagnosis of GH deficiency should be considered in all children with CP who are growing slowly.

States of GH deficiency are associated with abnormal body composition (increased fat mass and decreased muscle mass), reduced physical performance, altered lipid metabolism, increased risk of cardiovascular disease, osteopenia, and reduced quality of life. GH replacement therapy reduces adipose tissue, increases lean body mass, increases physical and cardiac performance, normalizes lipid metabolism, increases bone mineral density, and improves quality of life in adults with GH deficiency (Cuneo et al. 1998). In children with Prader–Willi syndrome, independent of GH status, treatment with GH has positive effects on body composition, fat utilization, physical strength and agility, in addition to linear growth (Carrel et al. 2000). Although no formal measurements were made, two of the three GH-treated patients that we report on

were noted to have improved strength and mobility. Lisset et al. (1998) reported on an adult patient with a long-standing neuromuscular condition who had previously been treated with GH during childhood. The patient showed marked improvements in mobility, independence, quality of life, and muscle power in a double-blind placebo-controlled trial of GH replacement, despite not having fulfilled the diagnostic criteria for GH deficiency.

For patients with CP, the beneficial effects of GH on bone metabolism could be extremely significant. GH and the mediator of its growth-promoting action, insulin-like growth factor-I, are key regulators of bone-cell function; they have therefore been considered as putative anabolic agents for the treatment of osteoporosis. In CP, decreased mobility and strength impair quality of life and compromise weight bearing, leading to cumulative losses in bone mineral. In children with CP, bone mineral density averages nearly 1SD below the age-matched normal means for both the proximal parts of the femora (–0.92SDs) and the lumbar spine (–0.8SDs; Henderson et al. 1995). This is clinically significant given that reduced bone density is strongly related to fracture risk (Johannsson and Ohlsson 1998). In addition to the direct effects of GH on bone, the trophic effects of GH on muscle are likely to lead to further improvement in bone health of children with CP through increased weight bearing and skeletal loading.

We report increased linear growth in three patients with CP who were treated with GH. These observations are confounded by several variables, including significant comorbidities in two of the patients and radiation and chemotherapy in one patient. It is also important to note that increased growth rate does not necessarily translate into increased final height. This limited report is intended to be a descriptive summary of our experience with GH treatment in CP and therefore no conclusions can be made about the efficacy of GH in this population. Clearly, long-term controlled studies are needed to evaluate the benefits and safety of GH treatment in children with CP and also to determine the prevalence of GH deficiency in this population. In summary, it is felt that GH therapy might be beneficial for children with CP and warrants further investigation.

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