GROWTH HORMONE IMPROVES MOBILITY AND BODY COMPOSITION IN INFANTS AND TODDLERS WITH PRADER-WILLI SYNDROME

AARON L. CARREL, MD, VICTORIA MOERCHEN, PhD, PT, SUSAN E. MYERS, MD, M. TRACY BEEK, MD, BARBARA Y. WHITMAN, PhD, AND DAVID B. ALLEN, MD

Objectives To determine the effect of growth hormone (GH) on body composition and motor development in infants and toddlers with Prader-Willi syndrome (PWS).

Study design Twenty-nine subjects with PWS (4-37 months of age) were randomized to GH treatment (1mg/m²/day) or observation for 12 months. Percent body fat, lean body mass, and bone mineral density were measured by dual x-ray absorptiometry; energy expenditure was measured by deuterium dilution; and motor constructs of mobility (M) and stability (S) were assessed using the Toddler Infant Motor Evaluation (TIME).

Results GH-treated subjects, compared with controls, demonstrated decreased percent body fat (mean, 22.6% ± 8.9% vs 28.5% ± 7.9%; P < .001), increased lean body mass (mean, 9.82 ± 1.9 kg vs 6.3 ± 1.9 kg; P < .001), and increased height velocity Z scores (mean, 5.0 ± 1.8 vs 1.4 ± 1.0; P < .001). Patients who began GH before 18 months of age showed higher mobility skill acquisition compared with controls within the same age range (mean increase in raw score, 284 ± 105 vs 206 ± 63; P < .05).

Conclusions GH treatment of infants and toddlers with PWS for 12 months significantly improves body composition and when begun before 18 months of age increases mobility skill acquisition. These results suggest that GH therapy instituted early in life may lessen deterioration of body composition in PWS while also accelerating motor development. (J Pediatr 2004;145:744-9)

Prader-Willi syndrome (PWS), described by Prader, Willi, and Labhart in 1956, is characterized by obesity, hypotonia, delayed motor skill acquisition, short stature, mental retardation, hypothalamic dysfunction, and hypogonadism.1 The obesity typically has an onset during childhood, after a period of neonatal failure to thrive.2,3 The genetic abnormality is located on chromosome 15 (q11-13) and may be a result of a deletion of the paternal allele, presence of maternal disomy, or imprinting center mutation.4 Other defining features observed in children with PWS include abnormal body composition with increased fat mass and low muscle tone, which is believed to be a result of decreased lean body mass.5,6 Infants with PWS typically demonstrate poor weight gain and hypotonia that precede hyperphagia and obesity. Even at this young age, body fat estimates, determined by skinfold thickness and confirmed by dual energy x-ray absorptiometry and deuterium dilution, are increased in these underweight infants.7,8 Growth hormone (GH) therapy instituted during childhood improves but does not normalize body composition,9,10 abnormally low energy expenditure,11 and strength and agility in PWS.12,13 We hypothesized that GH treatment of infants and toddlers with PWS could speed accretion of lean body mass, reduce accumulation of fat mass, improve motor function, and ultimately lead to a more normal body composition in childhood.

PATIENTS AND METHODS

Twenty-nine infants and toddlers with PWS 4 to 37 months of age, (mean age 15 ± 9 months; 13 females) were enrolled in the study after informed consent was obtained from the families.
a parent or legal guardian. All patients had a diagnosis of PWS confirmed by high-resolution cytogenetics, fluorescent in situ hybridization, and/or methylation studies. Seventeen subjects had deletion of chromosome 15q11-13, 11 had uniparental disomy, and 1 patient was diagnosed by an abnormal methylation test. Length/height measurements were obtained using a Harpenden stadiometer; subjects <2 years of age were measured supine on an infantometer (Perspective Enterprises, Portage, Mich). Stat GrowthCharts version 2.01 software (StatCoder.Com, Austin, Tex) was used to determine weight, height, and weight-for-height Z scores. Subjects underwent clonidine (0.15 mg/m²) stimulated GH testing following a 6-hour fast with blood drawn at 60 minutes for GH and insulin-like growth factor I (IGF-I) levels. GH was measured by chemiluminescent sandwich method; IGF-I levels were measured by radioimmunoassay by Nichols Institute, San Clemente, Calif. Fasting levels of insulin (chemiluminescent immunoassay), lipid profile (enzymatic), and free thyroxine (equilibrium dialysis), and thyroid stimulating hormone (immuno-chemilumino metric) were obtained at Esoterix Laboratories, Calabasas Hills, Calif. Leptin levels were performed using a double-antibody radioimmunoassay (Esoterix, Calabasas Hills, Calif).

Subjects were stratified by sex and age (4-18 months and 19-37 months) and then were randomized to GH (n = 15; Genotropin, Pfizer, New York, NY) 1 mg/m²/day, or to nontreatment control (n = 14). The cutoff of 18 months was used as a general distinction for age of ambulation in PWS. This dose is similar to that used in prior controlled studies of children with PWS.7,8 At baseline and at 12 months, percent body fat, fat free mass (FFM), and bone mineral density were measured by dual-energy x-ray absorptiometry (Lunar Prodigy by GE Medical System, Madison, Wis, version 3.6) in all subjects. In subjects evaluated at the University of Wisconsin Children’s Hospital, FFM and percent body fat also were determined by deuterium dilution (n = 14) calculated from the percent hydration expected for age and gender. For this, a loading dose of 0.15 g/kg of oxygen-18 water (Isotec Inc, Miamisburg, Ohio) and 0.1 g/kg of deuterium-labeled water (Cambridge Isotope Laboratory Inc, Andover, Mass) was given on Day 1. Urine samples collected in cotton diapers were obtained at −24 hours, then at 12, 24, 120, and 180 hours after dosing. Isotope analysis was performed at the Schoeller Energy Expenditure Lab, Department of Nutritional Sciences, University of Wisconsin-Madison, using all data points. The difference in elimination rates of the isotopes was used to calculate carbon dioxide production and total energy expenditure (TEE) using established equations. The average isotope dilution space ratio was 0.989, and the average difference in measured elimination rates per subjects was 0.05.

Motor constructs of mobility (M) and stability (S) were assessed at baseline, 6, and 12 months using the Toddler Infant Motor Evaluation (TIME).14 Our previous studies of GH treatment in older children with PWS had examined motor constructs of agility and strength using selected items from the Bruininks-Oseretsky Test of Motor Proficiency.15 Comparable performance measures for infants and toddlers in this study were identified using the M and S subtests of the TIME. According to the TIME, M is defined as the ability to move the body from one position to another, and S is defined as the dynamic control of the body within positions or during locomotion.

The TIME has empirically established internal consistency and test-retest stability. Additionally, the validity of the TIME was established in children with and without motor delays (including hypotonia, Down syndrome, and generalized motor delay). All motor testing was conducted by an evaluator who was blinded to the treatment status of each child. Raw scores (where scores reflect the complexity of motor skills, low to high) were used for comparisons of developmental trajectories beyond the baseline measurement. The Wilcoxon’s signed rank test (two-sided) was used to examine group differences for M and S, and analysis of covariance was used for age-adjusted comparisons between groups.

The performance of the infants and toddlers in this cohort was so low, such that standardized scores and percentiles were not sufficiently sensitive to detect changes in development across testing intervals (relative to chronological age). To address this lack of sensitivity for change within these infants and toddlers with PWS, the test’s author (Lucy J. Miller, personal correspondence) advised the use of raw scores (where scores reflect the complexity of motor skills) to quantify change within the persons in this study. In comparison with standard scores, and percentiles, raw scores allowed change to be quantified despite the delayed development associated with PWS. Performance relative to normative data was not relevant to the questions being asked, and all statistical comparisons were based on change scores. A high positive correlation between M and S at each observation and the lack of an exponential relationship between these constructs and change in time supported the reliability of using raw scores over time.16 Further, the use of raw scores allowed the TIME to be used without a ceiling effect of age. To adjust for effect of age on raw scores at each interval, absolute change in the raw scores were utilized.17 The Wilcoxon’s signed rank test (two-sided) was used to examine group differences for M and S, for analyses involving the entire cohort.

To examine whether age at the initiation of GH treatment in infants and toddlers with PWS would differentially affect motor outcome measures, the entire cohort was split into subgroups based on age at baseline: younger or older than 18 months of age. This distinction was identified a priori, and it was set as a guideline for an average age of attainment of “walking” motor milestones in PWS. This split reflected the expectation that effects of hypotonia would be most pronounced, and perhaps most amenable to treatment, early in motor development. Analysis of covariance was used for age-adjusted comparisons between groups.

RESULTS

Patient characteristics and study results are summarized in Tables I through III and are presented as mean ± SD.
Linear Growth and Growth Hormone Axis

At baseline, mean growth rate was 9.9 ± 2.5 cm/year (SD score for age = 1.3 ± 1.7), and height SD was −1.4 ± 1.1. Stimulated peak GH levels were 9.2 ± 5.7 ng/mL, (range 2.1-18.4 ng/mL). Baseline mean IGF-I level was 30 ± 18 ng/dL (~2 SD for age- and sex-matched normal range).

After 12 months, increase of height of GH-treated infants was 15.4 ± 2.3 cm compared with 9.2 ± 3.2 cm in nontreated infants (P < .001). Similarly, GH treatment was accompanied by an increase in growth velocity SD from 1.4 ± 1.8 to 5.0 ± 1.8 (P < .001 compared with baseline); whereas nontreated infants growth velocity SD was unchanged at 1.2 ± 1.4. Mean IGF-I in GH-treated infants was 231 ± 98 ng/mL compared with 51 ± 28 ng/mL in control subjects, P < .001. No difference in mean bone age progression was noted between groups.

Body Composition

Baseline body composition analysis (n = 29) revealed elevated body fat in PWS infants (mean 28.5% ± 7.3%) compared with reference data for non-PWS age-matched infants (mean 24.5% ± 4.0%; P < .05).15 Lean body mass was low (5.8 ± 1.9 kg), approximately 60% of total weight compared with ñ78% in reference data for age-matched control subjects.7 After 12 months of GH therapy, body fat decreased 4.8% ± 5.7% in GH-treated compared with untreated subjects whose percent body fat increased by 4.1% ± 4.6% (P = .001). Lean body mass increased significantly more in GH-treated patients versus nontreated controls (3.6 ± 0.5 kg vs 1.8 ± 0.7 kg; P < .001). No significant changes were seen in total body bone mineral density, which increased 14.1% ± 10.4% in GH-treated and 9.0% ± 6.9% (P = NS) in untreated patients.

Energy Expenditure

At baseline, children with PWS demonstrated reduced TEE compared with predicted values for age- and weight-matched non-PWS infants using the doubly labeled water method.16 TEE significantly increased after 12 months of GH therapy from 663 ± 149 kcal/day to 1025 ± 174 kcal/day versus 697 ± 124 kcal/day to 945 ± 341 kcal/day in controls (P < .05, compared with baseline and compared with untreated controls).

Motor: Mobility and Stability

There were no significant differences between groups for M or S skills at baseline. When the entire cohort of infants and toddlers was examined, there was no effect of GH on M or S skill acquisition during the first year of GH treatment (Table II). However, closer examination of the data revealed that relatively small sample size, paired with both the spread in the ages of patients and the high variability characteristic of this population, may have increased the probability of a type II error.

To examine whether a critical period existed for an effect of GH treatment on motor skill acquisition, the cohort was split into younger (<18 months of age) and older (>18 months of age) subgroups based on age at baseline. Age-adjusted comparisons between groups were then computed using baseline age and motor scores as covariates (Table III). Patients who received GH treatment before 18 months of age showed an improvement in M from baseline to 12 months that was significantly greater than the matched subgroup of patients in the control group (284 ± 105 and 206 ± 63, respectively; P < .05; Figure). Further examination of the data revealed that the change in M skill acquisition during the 6- to 12-month period of GH treatment in this subgroup accounted for this significance (160 ± 57 and 107 ± 52, treatment and control, respectively; P < .05). There was no effect of GH on S when adjusted for age at baseline for this younger subgroup, and there was no effect of GH on M or S for the older subgroup.

Carbohydrate and Lipid Metabolism

Before GH therapy, fasting plasma glucose and insulin levels were 81 ± 6.8 mg/dL and 4.8 ± 3.7 µIU/mL, respectively. After 12 months, no difference in fasting insulin was detected in either untreated (5.7 ± 7.1 µIU/mL) or GH-treated subjects (5.6 ± 7.1 µIU/mL) (P = NS). Total cholesterol decreased from 163 ± 34 to 159 ± 40 mg/dL in the GH treatment group;

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### Table I. Patient characteristics and 12-month data

<table>
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<th></th>
<th>GH treatment</th>
<th>Control</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age at baseline (mo)</td>
<td>13 ± 8</td>
<td>15 ± 10</td>
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</tr>
<tr>
<td>% female</td>
<td>50</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Mean % body fat at 12 mo</td>
<td>23.2 ± 8.9</td>
<td>32.7 ± 8.8</td>
<td>.03</td>
</tr>
<tr>
<td>Mean GV (cm/y)</td>
<td>15.3 ± 2.8</td>
<td>10 ± 2.5</td>
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<td>Mean GV 2 score</td>
<td>5.0 ± 1.8</td>
<td>1.4 ± 1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% change in muscle mass</td>
<td>61.5 ± 20.7</td>
<td>27.8 ± 14.1</td>
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<td>IGF-I (ng/mL)</td>
<td>231 ± 98</td>
<td>51 ± 28</td>
<td>&lt;.001</td>
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<td>IGF-I Z score</td>
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<td>&lt;.001</td>
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<tr>
<td>Leptin (ng/mL)</td>
<td>5.6 ± 7.2</td>
<td>14.4 ± 10.7</td>
<td>.02</td>
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</table>

*GV, growth velocity.*

### Table II. Group comparisons of baseline and change in M and S scores (TIME) at 6-month intervals from baseline to 12 months

<table>
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<th>Interval</th>
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<tr>
<td>M, 6-12</td>
<td>127</td>
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<td>NS</td>
</tr>
<tr>
<td>M, 0-12</td>
<td>246</td>
<td>187</td>
<td>NS</td>
</tr>
<tr>
<td>S, 0-6</td>
<td>48</td>
<td>58</td>
<td>0.07</td>
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<td>S, 0-12</td>
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<td>S, 0-12</td>
<td>146</td>
<td>167</td>
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</table>

Before GH therapy, fasting plasma glucose and insulin levels were 81 ± 6.8 mg/dL and 4.8 ± 3.7 µIU/mL, respectively. After 12 months, no difference in fasting insulin was detected in either untreated (5.7 ± 7.1 µIU/mL) or GH-treated subjects (5.6 ± 7.1 µIU/mL) (P = NS). Total cholesterol decreased from 163 ± 34 to 159 ± 40 mg/dL in the GH treatment group;
whereas the control group increased slightly from 170 ± 30 to 183 ± 43 mg/dL, although no statistical difference was noted. Further, no significant difference was noted between HDL-cholesterol, LDL-cholesterol, or triglycerides after GH treatment.

**Adverse Effects**

No changes in the prevalence of scoliosis were seen between the treatment and control groups. No other adverse effects were noted during this study.

**DISCUSSION**

Infants and toddlers with PWS commonly demonstrate hypotonia, associated with poor suck, poor feeding, compromised respiratory function, early failure to thrive, and delay in attainment of developmental motor skills. Body fat measurements are increased even in underweight infants with PWS. Early abnormalities in body composition in PWS, therefore, are present before the onset of characteristic hyperphagia and progressive obesity, and they are qualitatively similar to those observed in patients with GH deficiency (increased percent body fat and decreased muscle mass). Diminished GH secretion in PWS is well documented.

This is distinguished from reduced GH secretion observed in nutritional obesity by low IGF-I levels and abnormal body composition similar to that observed in patients with GH deficiency (increased percent body fat and decreased FFM). Interestingly, and in contrast to older children with PWS, our subjects did not consistently demonstrate low GH levels following clonidine provocation (16 of the subjects had levels <10 ng/mL). Possible explanations for this include:

1. clonidine is a stronger provocative stimulus for GH secretion in younger versus older children with PWS;
2. some manifestations of hypthalamic dysfunction present in PWS worsen with advancing age; and
3. increasing obesity during childhood has an additive, and perhaps exaggerated, suppressing effect on GH secretion in children with PWS. Prior studies using skinfold measurement reported increased subcutaneous fat in underweight infants with PWS. In this study, baseline body composition assessed by more accurate dual energy x-ray absorptiometry revealed significantly reduced lean body mass and increased body fat in infants with PWS when compared with published data for healthy non-PWS infants.

Prior studies by our group and others in older children have shown that prolonged treatment with GH can improve but not normalize marked body composition abnormalities in older children with PWS. These observations led us to question whether very early institution of GH therapy might:

1. prevent development of these severe body composition abnormalities and
2. lead to more normal body composition later in childhood than that achieved with later institution of GH therapy. In this randomized controlled trial, administration of GH to infants and toddlers with PWS at a daily dose of 1mg/m²/day increased lean body mass, reduced fat mass, and increased growth velocity. These changes were significant when compared with either changes in nontreated infants and toddlers with PWS and also when compared with baseline data in treated patients. No adverse effects were seen. Follow-up of this young cohort through childhood should provide answers to the second part of the hypothesis.

An equally important question is whether GH treatment would have a positive impact on the M and S aspects of motor development in infants and toddlers with PWS. Although this was first suggested in uncontrolled studies by Eiholzer and colleagues, this is the first controlled study of this question. Patients with PWS for whom GH

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**Table III. Age-adjusted (<18 mo of age vs >18 mo of age at baseline) comparisons of change in M and S scores using the TIME**

<table>
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<th>SD</th>
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<td>M, 6-12</td>
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<td>M, 0-12</td>
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<td>S, 6-12</td>
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<td>S, 0-12</td>
<td>141</td>
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<table>
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<td>70</td>
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<td>162</td>
<td>161</td>
<td>285</td>
<td>174</td>
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</table>

**Figure.** Age-related comparisons of change in mobility scores over 12 months revealed a significant effect for GH for infants who began GH before 18 months of age, an effect that was not observed in toddlers who began GH after 18 months of age.
treatment began before 18 months of age showed significant improvements in M compared with nontreated subjects. Measurement of motor change in these patients, however, was not straightforward. Several confounds have already been identified, including: (1) the number and age range of the patients studied was compounded by a large variability in the developmental motor performance of this population and (2) the TIME was more limited than we anticipated in its ability to document changes among infants and toddlers with marked delays in motor development (i.e., average performance at 0.1 percentile at each age level of the test) despite clinically apparent gains in test items across testing intervals. As already noted, this latter point required that we use the raw subtest scores for all patients. In comparison with standardized scores, the larger range of raw score values may have further increased the statistical variability of performance across the sample.

In addition to allowing examination of a possible age-related effect of GH treatment, splitting the cohort into infant and toddler subgroups reduced the variability in age in the sample. Within age-group, comparisons revealed significance for mobility skill acquisition in the subgroup that began GH treatment before 18 months of age. Although there was not a significant effect of GH treatment on stability, the ability to hold or be stable within postures is an aspect of motor control that often follows (in developmental time) mobility skill acquisition. It may be that GH treatment will exert its effect on the acquisition of postural stability at older ages. This proposition is supported by our previous study for GH treatment in older children. To our knowledge, formal motor evaluation of the effect of GH treatment on infants and toddlers has not previously been documented. Longer-term follow-up of the infants and toddlers treated in this present study may provide an answer to this question.

Although the results of this trial are encouraging, it is important to take into account possible complications of such treatment such as the invasive nature of this treatment (daily injections) as well as the prolonged exposure to GH therapy. Our experience has shown that for continued efficacy of GH therapy, over time GH dose escalation may be required, and it is conceivable that exposure to high-normal IGF-I levels is possible. It is also important to consider recent reports of deaths in children with PWS who were being treated with GH. These events have been concentrated in young children relatively early in the course of GH therapy. However, PWS is associated with a decreased life expectancy, and it is not known whether these reported deaths during GH therapy represent an increase in expected mortality. The exact cause of these deaths remains unknown, although evidence for respiratory obstruction/infection and severe obesity are reported in nearly all cases. Impaired ventilation responsiveness to hypercapnia and hypoxia are well documented in PWS, and lymphoid tissue growth during early GH therapy has been postulated to be a contributing factor. Interestingly, GH therapy has been shown to improve ventilation responsiveness to carbon dioxide in children with PWS. Consequently, it is possible that institution of GH therapy in infancy before development of obesity and increased tonsil/adenoïd growth might actually reduce any risk associated with adaptation to initial months of GH therapy later in childhood. In response to these incidents, recommendations for pre-treatment airway and sleep evaluation in all children with PWS considered for GH treatment are evolving.

Whether or not body composition improvements achieved at an early age continue remains to be seen. Continued treatment and careful prospective evaluation of this cohort will help determine whether very early institution of GH therapy in infants with PWS will lead to acceleration in attainment of developmental motor skills, that cumulatively, will result in body composition and physical function even closer to normal than we have observed in older GH-treated children with PWS.

REFERENCES


