Retrospective Study of the Potential Benefits and Adverse Events during Growth Hormone Treatment in Children with Prader-Willi Syndrome

Marc Fillion, MD, Cheri Deal, PhD, MD, and Guy Van Vliet, MD

Objective To assess the effectiveness of growth hormone (GH) treatment of children with Prader-Willi syndrome (PWS) in clinical practice.

Study design This was a review of 23 patients with PWS (14 males, 9 females) under age 18 years, 10 of whom (5 males, 5 females) had been treated with GH for periods between 0.1 and 5.5 years. All of these patients had a GH level < 5.5 μg/L on 2 GH stimulation tests.

Results In the 8 patients treated with GH for more than 1 year, median height velocity was 8.6 cm/year (range, 2.0 to 14.5 cm/year) during the first year, greater than that in the no-GH group (5.5 cm/year [range, 0.8 to 7.0 cm/year]) ($P < .05$). The evolution of body mass index (BMI) was similar in both groups, however (GH group: 3.1 standard deviation score [SDS; range, −2.5 to +6.7] at GH initiation and 3.3 SDS [range, −0.4 to +8.9] at last visit; no-GH group: 3.2 SDS [range, −0.3 to +6.4] at first visit and 2.6 SDS [range, −0.1 to +6.4] at last visit). In 3 patients treated with GH, sequential body composition analysis by dual-energy X-ray absorptiometry revealed no benefit. In both groups, stabilization or diminution of BMI was more often observed in children of highly educated parents. Two of the 10 patients treated with GH developed obstructive sleep apnea (OSA) 1 to 2 months after starting GH, 1 of whom died (reported previously).

Conclusions GH therapy in children with PWS in the clinical setting did not lead to any discernible improvement in BMI or body composition and appeared to be associated with OSA. Regardless of GH therapy, parental education was associated with better outcome. *(J Pediatr 2009;154:230-3)*

Prader-Willi syndrome (PWS) is characterized by hypothalamic dysfunction resulting in obesity, hypotonia, hypogonadism, delayed motor skill acquisition, behavioral abnormalities, and short stature.[1] Following a period of failure to thrive during infancy, obesity develops from hyperphagia amplified by reduced physical activity and decreased energy expenditure.[2] PWS is caused by genetic abnormalities on chromosome 15 (q11-13), including a deletion of the paternal allele (70% of cases), a maternal disomy (25% of cases), or imprinting center mutations (< 5% of cases).[3] In patients with PWS, body composition is characterized by reduced lean body mass (LBM) and increased fat mass, a pattern resembling that in patients with growth hormone (GH) deficiency as opposed to that of patients with exogenous obesity.[4-6] Thus, GH deficiency may contribute to the decreased linear growth and abnormal body composition in PWS.[7]

Consistent with this concept, GH therapy in patients with PWS has been found to increase height velocity (HV), decrease fat mass, and increase LBM, muscle strength (including that of respiratory muscles), and physical agility.[8] In addition, it increases ventilatory drive[9] and may reduce cardiovascular risk factors. Uncontrolled short-term GH trials in PWS demonstrating increased linear growth, decreased body fat, and increased muscle mass have been confirmed by randomized controlled trials (RCTs).[8-10] However, it should be emphasized that no RCT data comparing GH therapy to the absence of GH therapy in patients with PWS are available beyond 12 months; only dose-response studies are available after that point.[11] In addition, GH therapy has not been found to normalize body composition.[12]

See related article, p 225

BMI	Body mass index	OSA	Obstructive sleep apnea
GH	Growth hormone	PWS	Prader-Willi syndrome
HV	Height velocity	RCT	Randomized controlled trial
IGF	Insulin-like growth factor	SDS	Standard deviation score
LBM	Lean body mass		

From the Endocrinology Service and Research Center, Sainte-Justine Hospital, Montreal, Quebec, Canada and Department of Pediatrics, University of Montreal, Montreal, Quebec, Canada (M.F., C.D., G.V.V.).

The authors declare no conflicts of interest.

Submitted for publication Jun 11, 2007; last revision received Jul 11, 2008; accepted Jul 29, 2008.

Reprint requests: Guy Van Vliet, MD, Endocrinology Service and Research Center, Sainte-Justine Hospital, 3175 Côte Sainte-Catherine, Montreal, H3T 1C5, Quebec, Canada. E-mail: guy.van-vliet@recherche-ste-justine.qc.ca.

0022-3476/$ - see front matter

10.1016/j.jpeds.2008.07.058

Contrasting with these potential benefits, sudden death in children with PWS treated with GH have been reported, and a possible contribution of GH to these events has not been definitively excluded.[13] One possible factor is the development or worsening of obstructive sleep apnea (OSA).[14,15]

In the present study, we assessed the potential benefits and adverse events of GH treatment in children with PWS in a clinical setting. The main outcome was change in body mass index (BMI).

METHODS

In this retrospective study, all 28 patients with genetically confirmed PWS recorded in our endocrinology clinic database between 1990 and 2005 were potential subjects. Five patients were excluded from the study because they were under age 1 year (3 patients) and/or were seen only once at our clinic (2 patients). The 23 remaining patients included 14 males and 9 females. Sixteen patients had a deletion of chromosome 15 found on fluorescence in situ hybridization, 4 had a maternal disomy, and 3 had an imprinting center mutation. Patient age at the time of first visit to the clinic ranged from 1.3 to 13.5 years. Parent educational level was scored as follows: 1, high school completed; 2, college completed; 3, university completed (Table I; available at www.jpeds.com).

Ten patients (5 males, 5 females) were treated with GH for periods ranging from 0.1 to 5.5 years; they are designated the GH group. All 10 had GH levels < 5.5 μg/L in response to 2 stimulation tests (oral clonidine, 0.15 mg/m^2, and intravenous arginine, 500 mg/kg [maximum, 30 g]), but 7 of 10 had normal insulin-like growth factor (IGF)-1 levels. Counselling included a discussion of the option to treat with GH, with the decision made by each individual clinician based on the family's wishes. GH therapy was reimbursed because the patients met the criteria for GH deficiency in Quebec. In most cases, the dose was based on the patient's actual weight (median, 0.17 mg/kg/week [range, 0.08 to 0.21 mg/kg/week]). This dose was within the range traditionally used to treat GH deficiency in childhood (0.18 to 0.30 mg/kg/week) and similar to that used in other studies of children with PWS. On the basis of ideal body weight, the median GH dose was 0.25 mg/kg/week (range, 0.14 to 0.42 mg/kg/week).

Thirteen patients never received GH; they are designated the no-GH group. The baseline visit is defined as the visit at which the patient was first seen (for those not treated with GH) or at which GH therapy was started. The last visit is defined as the visit at which GH was stopped (end of therapy for those who stopped GH) or at which the patient was last seen (for those who never received GH or who are still being treated).

Height was measured with a wall-mounted stadiometer, and weight was measured using an electronic scale in light indoor clothing. BMI (calculated as weight [kg] ÷ height [m^2]), was calculated and converted to a standard deviation score (SDS) based on the SDS individual calculator for the 1990 British growth reference data (available at http://www.phsim.man.ac.uk/SDSCalculator/). At the discretion of the clinician, dual-energy x-ray absorptiometry (DEXA) (Lunar Prodigy; GE Healthcare, Chalfont St Giles, UK) for evaluation of body composition and fasting and 2-hour postprandial glucose and insulin were conducted in some patients. Polysomnograms initially were ordered only in patients exhibiting signs and symptoms of OSA, but now are ordered routinely, after the first death of a patient receiving GH therapy in late 2002. Spine films to screen for scoliosis were obtained at baseline and after GH therapy if clinically indicated.

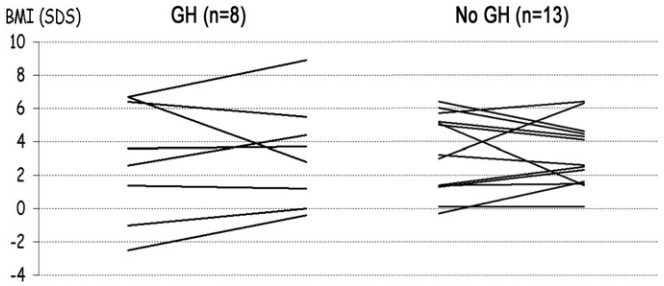

Figure. Evolution of BMI in 8 children with PWS treated with GH for more than 1 year (n = 8; *left*) or followed without GH (n = 13; *right*).

The data are presented as median and range. The patients treated with GH were compared with those who did not receive GH therapy by the Mann-Whitney *U* test. A *P* value $< .05$ was considered significant.

RESULTS

Table I summarizes the individual characteristics of all 23 patients in the study group. Eight of the 23 children had received GH therapy for 1 year or longer. The median age at baseline visit was 8.6 years (range, 1.3 to 13.5 years) in the GH group and 5.0 years (range, 2.0 to 13.0 years) in the no-GH group ($P = .43$). In the GH group, median HV was 8.6 cm/year (range, 2.0 to 14.5 cm/year) during the first year of GH therapy and 8.5 cm/year (range, 1.7 to 10.0 cm/year) during the second year of GH therapy. These HVs were higher than the corresponding values in the no-GH group (5.5 cm/year [range, 0.8 to 7.0 cm/year]; $P < .05$ and 5.1 cm/year [range, 1.0 to 8.0 cm/year]; $P = .05$).

The BMI distribution at baseline visit and last visit showed considerable variability in both the GH group and the no-GH group. BMI SDS was similar in both groups at baseline (GH group, +3.1 [range, −2.5 to + 6.7]; no-GH group, +3.2 [range, −0.3 to +6.4]; $P = .22$). At last visit, median BMI SDS was slightly (but not statistically significantly) higher in the GH group (+3.3 [range, −0.4 to +8.9]) than in the no-GH group (+2.6 [range, +0.1 to +6.4]) ($P = .11$). Stabilization or diminution of BMI SDS between the baseline and last visit was observed in 5 of 8 patients (62.5%) from the GH group and in 8 of 13 patients (61.5%) from the no-GH group (Figure).

Three patients in the GH group underwent evaluation of body composition by DEXA both before and then 7 to 16 months after starting GH therapy. The results are given in