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Long-term effects of recombinant human growth hormone therapy in children with Prader–Willi syndrome

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Abstract

Purpose of review—Recombinant human growth hormone (hGH) therapy in children with Prader–Willi syndrome (PWS) improves linear growth, body composition, physical strength and agility, and other metabolic parameters. These benefits must be weighed against potential adverse effects, including rare occurrences of sudden death. This review summarizes recent evidence important to a benefit–risk analysis of hGH use in children with PWS.

Recent findings—Studies consistently show that hGH improves stature, body composition, fat percentage and distribution, and other metabolic markers in children with PWS. Preliminary reports of improved cognitive development during hGH have also emerged. Scoliosis progression is influenced by growth rate, but frequency of occurrence and severity are not increased by hGH exposure. PWS genotype does not appear to affect response to hGH. Concerns about hGH-associated sudden death persist, but recent studies show either absence of change in sleep-disordered breathing or improved sleep cardiovascular function during hGH therapy.

Summary—Recent studies confirm and expand reported benefits of hGH therapy in children with PWS, including a possible salutary role in cognitive development. These findings support previous assertions that hGH can reduce morbidity and improve function in children with PWS, and suggest that potential risks of such treatment are favorably balanced by its benefits.

Keywords

body composition; cognitive development; growth; growth hormone; sleep-related disordered breathing

INTRODUCTION

Prader–Willi syndrome (PWS), first described by Prader, Willi, and Labhart in 1956, is characterized by hypothalamic dysfunction, distinctive facial features, neonatal hypotonia, delayed motor skill acquisition, poor growth in infancy with early feeding difficulties,

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Conflicts of interest

There are no conflicts of interest.

development of hyperphagia by 2–3 years of age, increased risk of obesity, short stature, and cognitive impairment [1,2]. Children with PWS also have a higher incidence of scoliosis, sleep-disordered breathing, and endocrine deficiencies [subnormal growth hormone (GH) secretion, central hypothyroidism and adrenal insufficiency, and hypogonadism] compared with non-PWS peers. The incidence of PWS is estimated to be 1 in 10 000–20 000 births. PWS was the first human disorder attributed to abnormalities in genetic imprinting, and the underlying genetic abnormalities are related to lack of paternally inherited gene expression of chromosome 15q11–13. Specific genetic aberrancies in PWS include deletion of the paternal allele (70% of patients), presence of maternal uniparental disomy (mUPD) of chromosome 15 (25–28%), imprinting center defects (2–5%), and translocation with PWS critical region (<1%) [1].

BACKGROUND OF HUMAN GROWTH HORMONE USE IN CHILDREN WITH PRADER–WILLI SYNDROME

Children with PWS display markedly abnormal body composition characterized by very high (predominantly subcutaneous) fat mass and very low lean body mass. Combined with short stature, relatively low IGF-1 (insulin-like growth factor-1) compared with BMI-matched peers, and low GH responses to provocation, this phenotype strongly resembles other GH deficiency (GHD) states. Recognition of GHD as a possible component of PWS led to trials of hGH therapy in children with PWS in an effort to improve body composition and height. Based on initial hGH therapy studies which showed rapid increase in linear growth rate and improved (but not normalized) body composition, energy expenditure, and motor development [3–6], the Food and Drug Administration approved hGH for use in PWS in June of 2000. However, early enthusiasm for hGH therapy in children with PWS was tempered by reports of a temporally associated increased risk of sudden unexpected death in children with PWS treated with hGH [7,8]. We review recent findings on the long-term effects of hGH in PWS patients and discuss how the results clarify questions regarding potential benefits and risks related to hGH therapy.

PROVEN AND POTENTIAL BENEFICIAL EFFECTS OF HUMAN GROWTH HORMONE IN CHILDREN WITH PRADER–WILLI SYNDROME

Recent studies confirm and expand reported benefits of hGH on growth, body composition, physical function, and metabolic health in children with PWS, and suggest a possible salutary role in cognitive development. Limited cost-effectiveness analyses have not rated hGH treatment for PWS favorably; however, these studies have focused exclusively on height, rather than quality of life effects of improved body composition and physical function [9]. At the same time, it is important to acknowledge that hGH therapy does not change the intrinsic abnormalities of PWS patients, so that life-long careful follow-up and monitoring is indispensable.

LINEAR GROWTH AND EVENTUAL HEIGHT

Although studies consistently showed that hGH increases short-term growth velocity in children with PWS, questions regarding long-term change in height (and whether significant long-term quality of life benefits accompanied change in height) remained. In a comparison of the linear growth in 21 children with PWS treated with hGH for 6 years with that of 27

age-matched and sex-matched children with PWS naive to hGH, the hGH-treated children exhibited significantly greater height (131 ± 2 vs. 114 ± 2 cm; $P < 0.001$) [10]. Similarly, 36 children with PWS demonstrated a significant increase in mean height of 1.2 standard deviations during 2–3 years of hGH therapy, and the increment of improvement did not differ significantly by sub-type (deletion vs. mUPD of 15q11–13 region) [11]. In addition, response to hGH in 56 other children with PWS also did not differ by genetic subtype (P=0.14) during the first year of therapy [12■]. With regard to eventual height attainment, children with PWS receiving long-term hGH therapy reached a mean adult height standard deviation score (SDS) of −0.3 (compared with −3.1 SDS in untreated controls, $P < 0.0001$). Together, these findings indicate that hGH is an anabolic hormone that supports growth rate and adult height attainment in children with PWS regardless of genetic subtype [13].

BODY COMPOSITION AND PHYSICAL FUNCTION

hGH is an anabolic hormone which supports development of lean muscle mass and stimulates lipolysis of fat for energy use. As noted earlier, GHD is associated with body composition abnormalities (increased fat mass, diminished lean mass) that are typical for PWS and could be reasonably expected to improve with hGH therapy; indeed, numerous studies have shown beneficial effects of hGH on body composition and physical function in PWS. Perhaps one of the most convincing is a recent comparison of children with PWS treated with hGH for 6 years with age-matched and sex-matched PWS peers never treated with hGH [10]. This study demonstrated not only significantly lower body fat percentage (mean 36.1 ± 2.1 vs. 44.6 ± 1.8%, $P < 0.01$) and increased lean body mass, but also improved physical function manifested by greater motor strength [increased standing broad jump (22.9 ± 2.1 vs. 14.6 ± 1.9 in., $P < 0.001$) and more sit-ups (12.4 ± 0.9 vs. 7.1 ± 0.7, $P < 0.001$)], in hGH-treated vs. nontreated children with PWS (Table 1).Additionally,CT (computed tomography) imaging reveals that hGH-treated PWS patients show significant decreases in subcutaneous fat volume (−20%, $P = 0.01$) with a trend toward lower visceral fat (−25%, $P = 0.18$) and thigh fat (−12%, $P = 0.08$) after 2 years of hGH treatment [14]. In a similar, but prospective, study utilizing CT imaging, PWS patients treated with hGH deposited less visceral fat at the level of the umbilicus than the untreated controls [15■]. However, after discontinuation of hGH therapy, visceral fat deposition increased at a tempo similar to those never treated with hGH [15■]. These results indicate that body composition and physical function in children with PWS are improved, but not normalized, by long-term hGH treatment, and that maintenance of hGH-mediated body composition improvement appears to be dependent on continued treatment.

METABOLIC HEALTH

GH-deficient individuals typically demonstrate elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides with low concentrations of high-density lipoprotein (HDL) cholesterol. Following hGH treatment, these individuals exhibit improved lipid profiles (decreased total cholesterol and LDL cholesterol with increases in HDL cholesterol) [16]. A similar effect has been demonstrated in children with PWS who, following long-term hGH treatment, showed significantly increased HDL cholesterol (58.9 ± 2.6 vs. 44.9 ± 2.3 mg/dl, $P < 0.001$) and decreased LDL cholesterol (100 ± 8 vs. 131 ± 7 mg/dl, $P < 0.01$) compared with nonhGH-treated children with PWS (Table 1) [9].

Additionally, although hGH is a counterregulatory hormone that promotes insulin resistance, significant improvements in body composition (decreased fat mass and increased lean body mass) in PWS patients treated with hGH could also be expected to potentially improve insulin signaling and sensitivity. In this regard, some investigators have reported a decrease in frequency of impaired glucose tolerance in hGH-treated youth with PWS during 3 years of hGH therapy [11]. However, when prepubertal PWS children receiving long-term hGH were compared with age-matched nontreated PWS children, small numerical (but statistically insignificant) increases were seen in fasting glucose and insulin (Table 1) [10]. Thus, existing evidence suggests that hGH therapy improves lipid profiles but does not predictably or consistently benefit glucose metabolism in children with PWS.

COGNITIVE FUNCTION AND DEVELOPMENT

Cognitive impairment and developmental delay are a feature in children with PWS. Preliminary studies suggest that hGH may improve cognitive development in infants with PWS early in life [17]. A recent prospective trial involved 50 prepubertal children with PWS (3.5–14 years old) who were randomized to receive either 2 years of hGH therapy or no treatment; during the study period, hGH-treated individuals maintained consistent (though below normal) SDSs on tests of cognitive function (i.e., kept pace with non-PWS peers, but did not catch up), whereas untreated children demonstrated deterioration in SDS in certain cognitive areas [abstract verbal reasoning −0.7 SDS (confidence interval, CI, −1.3 to 0.03 SDS, $P = 0.04$) and vocabulary −0.7 SDS (CI 1.3 to −0.07 SDS, $P = 0.03$)] [18■■]. When compared with their own baseline function, all children with PWS treated with hGH for 4 years showed significant improvement in abstract verbal reasoning [+0.4 SDS (CI −0.1 to 0.7 SDS, $P = 0.01$) and visuospatial skills (+0.3 SDS, CI −0.07 to 0.6 SDS, $P = 0.01$)]; however, mean vocabulary and total IQ testing results did not change significantly with hGH [18■■]. These findings in children complement a study of PWS adults naïve to hGH in which higher IGF-1 values (i.e., perhaps suggesting greater endogenous GH action) correlated with improved visual pattern recognition and reaction time [19]. Clearly, the roles of GH and IGF-1 in cognitive function, brain plasticity, and learning merit further investigation. At present, evidence suggests that hGH treatment does not normalize cognitive abilities of children with PWS, but may reduce the disparity in cognitive ability compared with non-PWS peers that otherwise would increase over time.

POTENTIAL ADVERSE EFFECTS OF HUMAN GROWTH HORMONE THERAPY IN CHILDREN WITH PRADER–WILLI SYNDROME

Concerns about potential adverse effects of hGH therapy in children with PWS have focused on scoliosis, carbohydrate metabolism, and unexpected cardiorespiratory events, but ongoing analysis suggests that potential risks of hGH treatment are favorably balanced by its benefits.

Scoliosis—Scoliosis is very common in patients with PWS, prompting concern over whether hGH-induced acceleration of linear growth might influence the incidence or progression of scoliosis in PWS patients. Noncontrolled studies report that scoliosis frequency increases during long-term treatment with hGH [11], an expected finding in a group of growing children at high risk. In contrast, in controlled studies comparing hGH-

treated and non-treated children with PWS over a 6-year time frame, there was no difference in the rate of development or severity of scoliosis between groups [10]. In addition, when early evidence for scoliosis is carefully screened for at the time of hGH initiation, the new development of scoliosis in children with PWS appears unlikely [20■]. Interestingly, progression of scoliosis during hGH therapy has been associated with lower increases in paravertebral muscle volume measured by CT, suggesting muscle growth may prevent scoliosis progression. While this raises the question of whether hGH-mediated increase in muscle mass and strength might actually decrease the occurrence or progression of scoliosis, there are no data yet to support this effect in PWS patients. Taken together, studies indicate that monitoring for scoliosis in this at-risk population, whether treated with hGH or not, is important, and hGH does not significantly increase the risk of scoliosis development.

Glucose intolerance—Compared with similarly obese individuals without PWS, hGH-naive PWS children and adolescents are actually relatively insulin sensitive. This may be partially attributed to the predominantly subcutaneous (rather than visceral) deposition of fat, but also to reduced counterregulation by endogenous GH. As a result, there has been concern that hGH therapy could unmask and/or exacerbate glucose intolerance in PWS recipients. As mentioned above, comparison of long-term hGH-treated and non-treated school-aged children with PWS showed no evidence of significantly higher fasting insulin, glucose, or homeostatic model assessment-insulin resistance (HOMA-IR) levels attributable to hGH treatment (Table 1) [10]. A study of older children with PWS (many of whom became pubertal, a period of physiologic increase in insulin resistance), indicated that mean fasting insulin and HOMA-IR increased in PWS children treated with hGH; however, fasting insulin and HOMA-IR levels remained within normal ranges. Further, the number of children with impaired glucose tolerance actually decreased from five to zero over the 3-year study [11]. In summary, although hGH treatment has the theoretical potential to increase insulin resistance, clinically significant changes in measures of insulin resistance (e.g., fasting insulin) or more frequent development of impaired glucose tolerance has not been found in children with PWS receiving hGH.

Cardiorespiratory compromise and sudden death—In 2002, the death of a 6-year-old boy with PWS following 4 months of hGH therapy was presented [8]. This report was followed by similar reports of death while on hGH therapy, and a larger review in 2008 of 64 deaths of youth (<1 month to 19 years old) with PWS [21]. Importantly, the rate and causes of death in the 64 cases did not differ significantly between hGH-treated and untreated patients, and it was found obese youth with PWS and those with respiratory insufficiency or illnesses were at increased risk of death. Interestingly, the review demonstrated that 75% (21/28) of deaths in PWS youth treated with hGH occurred within 9 months of starting hGH, a pattern of clustering not seen in youth not treated with hGH. Concern regarding the temporal association of more frequent unexpected sudden death in PWS patients on hGH therapy has continued to drive investigation into whether a causal relationship may exist [7,8]. Answering this question is made extremely complex by the tendency for individuals with PWS to demonstrate morbid obesity, obstructive sleep apnea (OSA), autonomic instability, reduced ventilator sensitivity to hypoxia and hypercarbia, and increased baseline rates of sudden unexplained death – all likely related to underlying

hypothalamic dysfunction and its complications. A recent study reported that, out of 15 children with PWS, two developed severe OSA evident on polysomnography within 6 weeks of starting GH therapy [22■■]. Importantly, the 13 of 15 children who did not exhibit significant sleep-related disordered breathing at baseline or 6 weeks after initiation of GH therapy remained without significant sleep-related disordered breathing after 2 years of GH therapy, suggesting that most children with PWS do not develop significant sleep-related disordered breathing on hGH.

In addition, children with PWS treated with hGH have demonstrated improvement in respiratory muscle strength response to carbon dioxide concentration, and nocturnal coupling of heart rate and blood pressure, all of which suggest improved cardiovascular and/or autonomic function [23■,24,25]. Thus, evidence indicates that cardiorespiratory complications from hGH do not develop in most PWS children receiving hGH, and that the observed cases of sudden death are more likely unrelated to hGH therapy [21]. Nevertheless, as this issue remains unresolved, current general recommendations suggest performance of clinical and polysomnographic evaluation for sleep-related disordered breathing prior to starting hGH therapy. If disordered breathing is detected, it is recommended to withhold hGH until significant breathing abnormalities are corrected with surgical and/or CPAP (continuous positive airway pressure) and/or weight loss interventions. Finally, once hGH therapy is started, ongoing clinical monitoring for breathing changes or sleep disturbances during hGH therapy is recommended.

CONCLUSION

hGH treatment increases height and improves body composition, physical function, and metabolic health in children with PWS. Particularly when initiated early in life, hGH significantly and favorably alters the natural history of PWS with low (but perhaps not negligible) risk of adverse effects. Potential hGH-mediated advancement in motor and cognitive development, though encouraging, requires further study. Questions remain about necessity of continuing hGH therapy into adulthood, its cost-effectiveness, and consent (or refusal) for cognitively disabled individuals. Whether treated with hGH or not, all individuals with PWS, given their complexities, deserve expert care to maximize health outcomes and quality of life.

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KEY POINTS

- hGH improves growth, body composition, and markers of metabolic health of infants and children with PWS.
- Response to hGH does not appear to be influenced by PWS genotype (e.g., paternal deletions vs. maternal uniparental disomy of 15q11–13 region).
- Cognitive and motor skill development of infants and children with PWS may be improved by hGH therapy, but more studies are needed.
- hGH therapy, in general, does not adversely affect scoliosis or carbohydrate metabolism in children with PWS; however, individual monitoring is important.
- In infants and children with PWS, sleep-related disordered breathing due to hGH therapy, and potentially instances of unexplained respiratory death, are rare, but screening for and correction of disturbed sleep-related breathing remains important.

Table 1

Effects of long-term recombinant human growth hormone therapy on height, body composition, motor function, and lipid profile in children with Prader–Willi syndrome

	GH-naive cohort (n = 21) Mean ± SE[a]	Early-treatment cohort (n = 27) Mean ± SE[a]	P value[b]
Percentage body fat	44.6 ± 1.8	36.1 ± 2.1	0.006
Fat-free mass (kg)	16.7 ± 0.9	24.1 ± 1.1	<0.0001
Height (cm)	114.5 ± 1.8	131.4 ± 2.1	<0.0001
Height z-score	–1.6 ± 0.3	1.2 ± 0.2	<0.0001
Standing broad jump (in.)	14.6 ± 1.9	22.9 ± 2.1	0.012
Sit-ups	7.1 ± 0.7	12.4 ± 1.0	0.0003
HDL cholesterol (mg/dl)	44.9 ± 2.3	58.9 ± 2.6	0.0005
LDL cholesterol (mg/dl)	131.3 ± 7.1	100.2 ± 8.0	0.0099
Total cholesterol (mg/dl)	189.9 ± 7.3	177.3 ± 8.2	0.29
Triglycerides (mg/dl)	68.4 ± 10.6	94.2 ± 11.9	0.14
Fasting insulin	7.1 ±1.3	10.2 ± 1.5	0.14
HOMA-IR	1.4 ± 0.3	2.1 ± 0.3	0.1

GH, growth hormone; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; LDL, low-density lipoprotein.

Adapted from [9].

[a] Least squares mean, adjusted for age and sex.

[b] Based on two-sided t-test.