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Growth Hormone Treatment Completely Normalizes Adult Height and Improves Body Composition in Prader-Willi Syndrome: Experience from KIGS (Pfizer International Growth Database)

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Key Words
Prader-Willi syndrome · Growth hormone · Near-adult height · Body composition

Abstract
Background: Abnormal body composition, with low muscle mass and increased fat mass, as well as short adult stature are common features in Prader-Willi syndrome (PWS), as in growth hormone (GH) deficiency. ***Methods:*** We followed a cohort of 22 genetically verified patients with PWS from the start of GH (Genotropin®) treatment at the median age of 6.9 years (4.9–11.3) to near-adult height at 18.1 years (16.4–21.2). The patients were treated with a median GH dose of 0.03 mg/kg/day (0.02–0.03) for a median duration of 10.2 years (6.9–11.5). ***Results:*** All patients reached near-adult height within midparental height median –0.5 SDS (–1.4 to 0.7) and 0.9 SDS (0.1–1.9) for girls and boys, respectively. The body composition improved but did not normalize. Only 7 of the 22 patients were reported to be in puberty. None of the patients were reported to be on sex hormone substitution which might contribute to not reaching a normal body composition. No serious side effects were reported when the caloric intake was controlled to maintain an appropriate body weight. ***Conclusion:*** GH treatment in children with Prader-Wili syndrome normalizes adult height and improves body composition.

Introduction

Prader-Willi syndrome (PWS) is a complex neurogenetic disorder characterized by both mental and physical abnormalities. These include short adult stature, muscular hypotonia, abnormal body composition, excessive appetite with progressive obesity if the caloric intake is not restricted, hypogonadism, mental retardation, behavioural abnormalities, respiratory and sleep disturbances (including sleep apnoea) and dysmorphic features [1]. PWS arises from loss of expression of paternally inherited genes in the region q11–q13 on chromosome 15 [2] and is believed to result in dysfunction of several hypothalamic centres [3, 4].

Subjects with PWS have compromised growth and abnormal body composition with increased fat mass, decreased lean body mass (LBM) and low bone density resembling a growth hormone (GH)-deficient status [5]. GH treatment is in many countries an approved treatment option in children with PWS. It has been shown to improve longitudinal growth and to have additional beneficial effects on body composition [6–9]. Previous studies have shown short-term beneficial effects of GH treat-

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Table 1. Characteristics of the patients with PWS at start of GH treatment (median and 10th to 90th percentile)

	Boys	Girls
Number of patients	13	9
Age (range), years	6.2 (4.9–8.9)	8.2 (4.4–12.9)
Height SDS	–1.4 (–2.3 to –0.2)	–1.8 (–4.0 to –1.1)
Height syndrome-specific SDS	0.2 (–0.5 to 1.0)	–0.6 (–1.8 to 0.1)
Height SDS-midparental height SDS	–1.2 (–3.2 to –0.2)	–2 (–4.1 to –1.0)
BMI SDS	2.3 (0.6 to 3.8)	1.5 (0.9 to 2.1)
Body fat percentage (range)	39 (27–50)	36 (26–51)
LBM SDS	–1.9 (–3.0 to –1.4)	–3.1 (–5.0 to –0.9)
BMD SDS	–0.3 (–2.0 to 1.6)	–0.8 (–1.5 to 1.9)

ment in PWS. By using the KIGS (Pfizer International Growth Database; see below) we were able to follow until near-adult height the cohort of children who participated in the controlled randomized Swedish-Danish study by Lindgren et al. [10].

Patients and Methods

Patients

The effects of GH (Genotropin®; Pfizer Inc., New York, N.Y., USA) treatment in 22 children (13 boys) with genetically verified PWS (deletion in all cases except 1 who has a maternal disomy and 1 who has a translocation), who started treatment prepubertally at a median age of 6.9 years (4.9–11.3), were followed until near-adult height. The children participated initially in a controlled randomized trial which was conducted to assess the effects of GH treatment on growth, body composition and behaviour [10]. The children were randomized to a control group or to a GH treatment group (0.03 mg/kg/day) during the 1st year in the trial. The year thereafter the control group started treatment with GH (0.06 mg/kg/day) while the initial GH treatment group continued with the initial GH dose. After 2 years in the trial, all children discontinued GH treatment for 6 months and then restarted with GH at a standard dose (0.03 mg/kg/day). At restart, the children were included in the KIGS.

Prior to GH treatment, the GH/IGF-I status of all children was evaluated and found to be low: mean 24-hour GH sampling showed a median level of 0.7 μg/l (0.2–1.7) and IGF-I median –1.6 SDS (–2.6 to –0.9). All children were retested 3 weeks after discontinued GH therapy and both GH and IGF-I levels were as low as before GH treatment.

The body composition was evaluated by dual-energy X-ray absorptiometry (DEXA) prior to the start of GH treatment and after 1 and 7 years of GH treatment. All children had contact with a dietician and were put on a reduced caloric intake of approximately 800–1,400 kcal/day.

The Ethics Committee of the Karolinska Institute, Stockholm, Sweden, approved the randomized controlled study and the collection of data in the KIGS (Kabi International Growth Study, now administered by Pfizer Inc.). Patients and parents consented to participate in the study and in the KIGS.

Methods

The height, weight and body mass index (BMI) standards used were those of Karlberg et al. [11], Freeman et al. [12] and Cole et al. [13], respectively. The height and weight syndrome-specific standards used were those of Hauffa et al. [14]. Fat mass, LBM and bone mineral density (BMD) standards used were those of van der Sluis et al. [15]. Body composition, estimating body fat, lean body fat and BMD, was determined by DEXA according to standard procedures [16]. The GH assay used, after blood sampling every 30 min for 24 h, was an in-house radioimmunoassay [17]. The IGF-I levels were measured by radioimmunoassay after acid-ethanol extraction [18] and were standardized for age and gender [19].

Statistics

Values are given as medians and 10th and 90th percentiles.

Results

At the start of GH treatment, the median height was –1.6 SDS (–3.5 to –0.3), which was also –1.6 SDS (–3.5 to –0.2) below midparental height (MPH). The BMI was 1.7 SDS (0.8–3.3). Assessed by DEXA, the LBM was –2.6 SDS (–4.0 to –0.9), the fat/lean ratio was 0.8 (0.4–1.1) and the body fat percentage was 39 (27–51), while the BMD was –0.4 SDS (–2.0 to 1.9; table 1).

After 1 year of GH treatment, the height had significantly increased to –0.4 SDS (–2.3 to 1.5) and height compared to MPH had improved similarly. The BMI had significantly decreased to 1.0 SDS (0.2–2.5; $p < 0.05$). The LBM had significantly improved to –1.4 SDS (–2.6 to 0.1; $p < 0.05$). Fat/lean ratio and body fat percentage had decreased significantly to 0.35 (0.2–0.8; $p < 0.05$) and 24 (18–42; $p < 0.05$), respectively. No significant change of the BMD was found.

Seven children (4 girls) were reported to have entered puberty, defined as testis ≥4 ml for boys and Tanner stage 2 breast development for girls, at a median age of

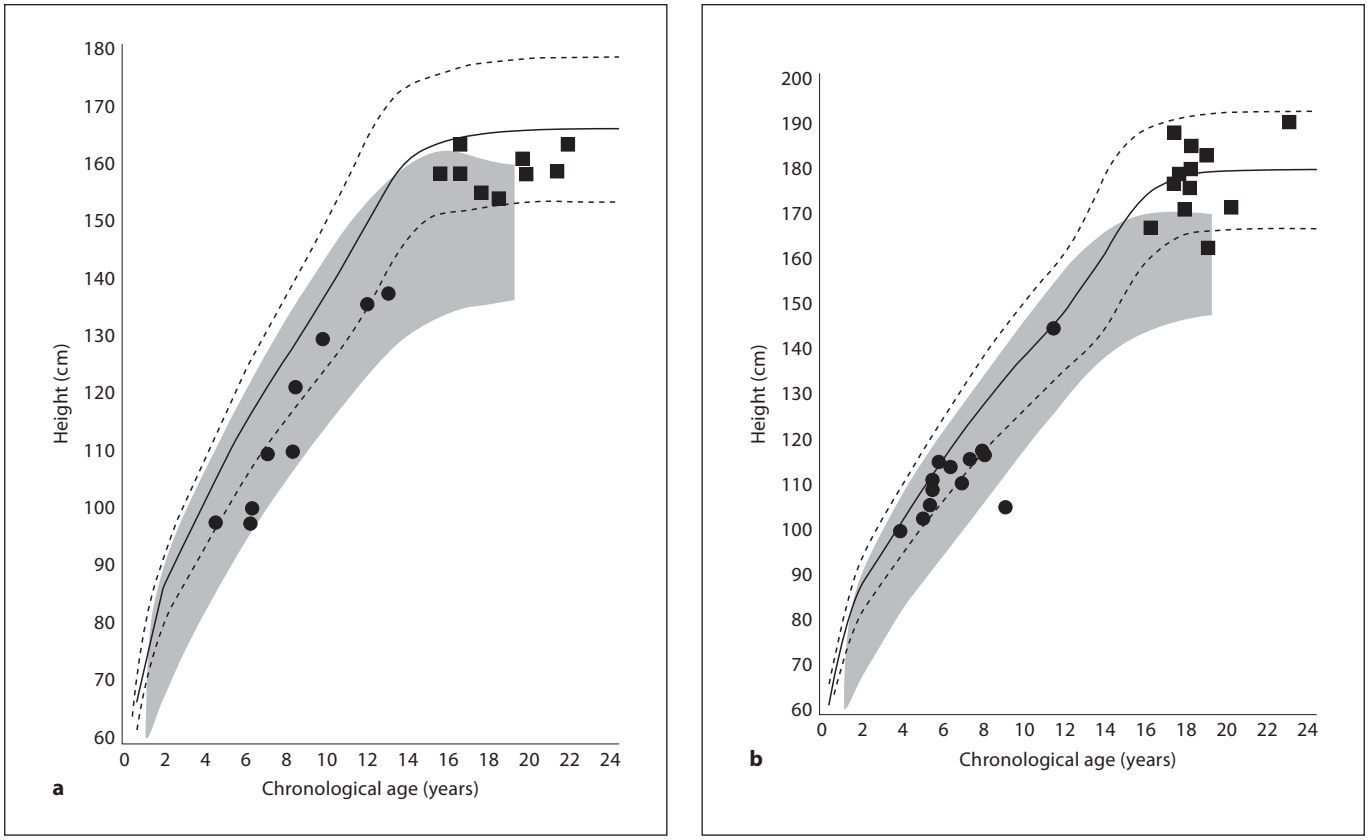

Fig. 1. Girls (**a**) and boys (**b**) with PWS. ● = Height at start of GH treatment; ■ = near-adult height. The solid line represents the growth of a normal population ± 2 SDS [11] and the shaded area the syndrome-specific growth [14].

11.2 years (10.2–13.5) for both genders. The height at start of puberty compared to MPH was for the females –0.2 SDS (–1.8 to 0.3) and for the males 2.3 SDS (1.5–2.7). The BMI at start of puberty in girls was 1.0 SDS (0.3–2.0) and in boys 1.9 SDS (1.6–2.1).

The median age of reaching near-adult height, defined as growing <2 cm/year, was 18.1 years (16.2–21.2) for both genders. The near-adult height for girls was –0.5 SDS (–1.2 to 0.1) and for boys 0.9 SDS (–0.2 to 2.2). The near-adult height compared to MPH for girls was –0.5 SDS (–1.4 to 0.7) and for boys 0.9 SDS (0.1–1.9). The girls and boys had reached a height of 1.8 SDS (0.9–2.7) and of 3.0 SDS (1.1–5.0), respectively, above the syndrome-specific final height (fig. 1). The BMI at final height was 2.2 SDS (0.5–2.9) and 1.6 SDS (0.1–2.7) for girls and boys, respectively. The median duration of GH treatment was 8.2 years (5.8–11.7) and 10.2 years (6.9–11.5) for girls and boys, respectively, with a median dose of GH of 0.03 mg/kg/day. After 7 years of GH treatment we performed DEXA scans in 17 of these patients, showing that the LBM was –1.7 SDS (–3.3 to 0.5; fig. 2) for the whole group, while the LBM was –2.7 SDS (–3.3 to 1.8) and –1.6 SDS (–3.2 to –0.5) for girls and boys, respectively. The fat/lean ratio was at the same level as at the start of GH and body fat percentage showed a similar development: 0.7 (0.2–1.0) and 40 (24–46), respectively (fig. 3). The BMD after 7 years of GH treatment had improved to ±0 SDS (–2.0 to 2.0) for the whole group, while the BMD was 0.4 SDS (–2.0 to 2.0) and –0.5 SDS (–1.5 to 1.1) for boys and girls, respectively.

Few adverse events were reported during this treatment. Two patients developed glucose intolerance and type 2 diabetes mellitus when their caloric intake went out of control and their weight increased rapidly within 6 months (>10 kg). When their weight was reduced, their glucose levels normalized. One patient had a worsening of her scoliosis and needed surgical intervention.

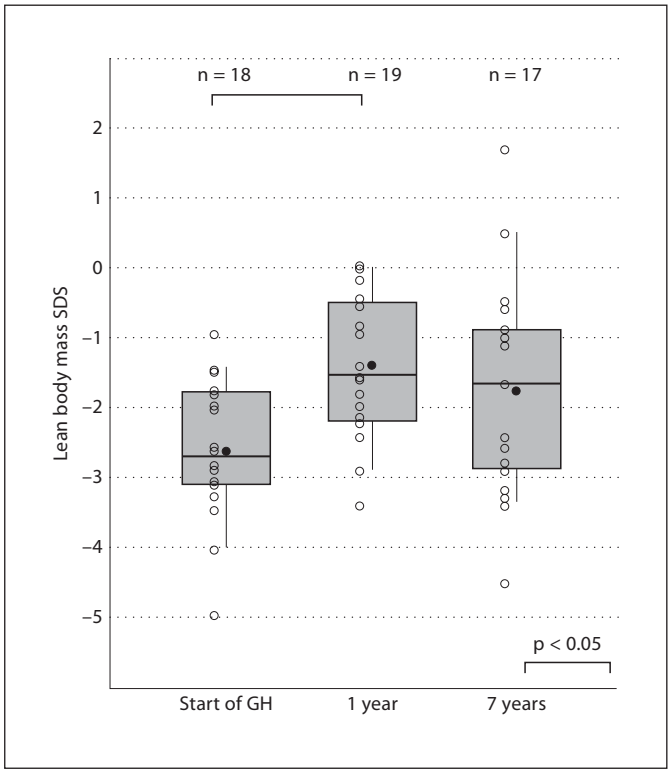

Fig. 2. Cross-sectional presentation of lean body mass SDS in children with PWS at start of GH and after 1 and 7 years of GH treatment. The box plots represent 10th to 90th percentiles.

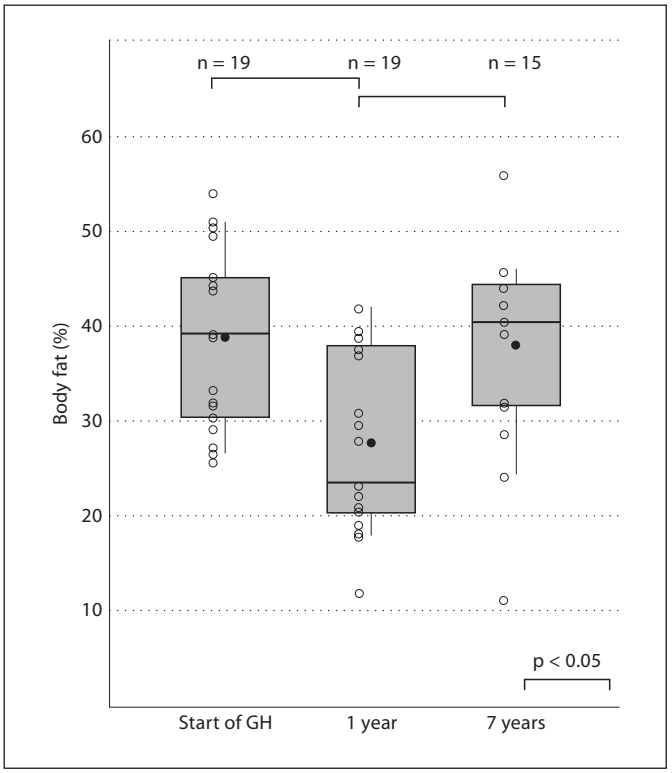

Fig. 3. Cross-sectional presentation of body fat percentage in children with PWS at start of GH and after 1 and 7 years of GH treatment. The box plots represent 10th to 90th percentiles.

Discussion

This study of children with PWS in the KIGS treated with GH showed an astonishingly good effect on longitudinal growth, promoting adult height which was reached within MPH when starting GH treatment at 6.9 years of age. However, it is interesting that the body composition is not normalized at near-adult height. Although the LBM has improved at near-adult height, it is still low. Body fat percentage and fat/lean ratio improved during the 1st GH treatment year but at near-adult height returned to similar levels as before the start of GH treatment. Interestingly, there is a gender difference, not significant, at the start of GH treatment and at near-adult height regarding height, BMI and LBM, although none of the subjects were on sex steroid replacement therapy. However, the males started GH treatment at an earlier age and were treated with GH for 2 more years than the girls.

The natural course of the syndrome is a massive increase of fat mass with age [20] and it seems to be possible to avoid this with GH treatment. The BMD also ameliorated with long-term GH treatment. Safety during long-term treatment with GH does not seem to be an issue if the body weight is maintained at an appropriate level.

The standard dose of GH used seems appropriate for growing, but does not seem to be sufficient to improve body composition, to increase LBM and to decrease fat mass. In previous studies, Carrel et al. [8] showed that a higher dose of GH (>1 mg/m^2/day, corresponding to 0.033 mg/kg/day) had better effects on body composition with decreased body fat and Eiholzer et al. [21] showed that GH treatment in children with PWS improved LBM but did not normalize it.

The children participating in this study were all put on a restricted caloric intake which was easier to follow when the children were young, as they were more closely supervised by their caretakers. With increasing age and during adolescence, the children become more independent and are faced with all the tempting food available today. In our experience, it is hard to follow a diet during adolescence; thus, it is hard for many adolescents with PWS to maintain their weight although they follow a diet at home.

In this study, the body fat percentage was reduced during the first years of GH treatment when the children were supervised but after 7 years of GH therapy, when the children are in adolescence, it is difficult to supervise their caloric intake. This is a possible explanation why they did not further reduce their fat mass. However, their BMI at near-adult height had not increased to the same levels as has been shown in previous studies of subjects with PWS without GH treatment [20]. These children were more than 6 years of age at the start of GH treatment so it is possible that, with an earlier diagnosis which will result in an earlier start and a longer time of GH therapy in combination with appropriate sex steroid replacement, subjects with PWS will have a better improvement of their body composition in the future.

The fact that individuals with PWS have a late and incomplete puberty may also play a role in a not normalized body composition. They might have an early adrenarche but the gonadal puberty is blunted and incomplete in most subjects. At near-adult height none of the subjects had been reported by their physicians to have completed puberty and none of the subjects in this study were reported to be treated with sex steroid replacement therapy. The lack of sex hormones has not only an influence on growth but also on the poor development of the body composition, especially LBM, through the close interaction between GH and sex steroids [22]. So it is possible that the outcome regarding body composition and growth for subjects with PWS will further improve in the future as sex steroid replacement therapy is advised to start at an appropriate age. The hypogonadism found in subjects with PWS probably contributes to the low BMD, as has been shown for other patient groups [23].

GH treatment in children and adolescents with PWS seems to be a safe treatment. In the present cohort, 2 adolescents with PWS developed type 2 diabetes when their body weight increased rapidly. When the body weight was reduced in these patients, the glucose homeostasis normalized. Both restarted GH therapy after an interruption of approximately 6 months and 1 of the patients also continued with metformin. Previous studies have shown that children with PWS have an increased insulin-sensitivity, as do GH-deficient children [24, 25]. Thus the development of type 2 diabetes seems to be more dependent on the amount of fat mass of the individual than on the syndrome itself.

Scoliosis is a common complication in individuals with PWS due to their muscular hypotonia [26]. It has also been reported to increase with rapid growth as during GH treatment. However, the development of scoliosis in children and adolescents with PWS during GH treatment did not show an increased frequency compared to non-GH-treated subjects with PWS.

To conclude, GH treatment of the children with PWS in the KIGS until near-adult height improves growth and promotes adult height. The body composition is improved with GH treatment although LBM and body fat percentage do not reach normal levels. Further long-term and follow-up studies of the effects of sex steroids on body composition in subjects with PWS and the synergistic effects with GH are needed.

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