Original Paper

Hormone Research

Horm Res 2000;53:185–192

Received: December 22, 1999
Accepted after revision: June 14, 2000

Growth Hormone Normalises Height, Prediction of Final Height and Hand Length in Children with Prader-Willi Syndrome after 4 Years of Therapy

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Key Words

Prader-Willi syndrome · Prader-Labhart-Willi syndrome · Growth hormone therapy · Growth · Syndromal obesity · Weight for height · Hand length · Foot length

Abstract

Background: Based on the reported favourable effects of growth hormone (GH) treatment on growth and body composition in Prader-Labhart-Willi syndrome, we studied age dependency and the long-term effects on growth dynamics to elucidate the assumed hypothalamic GH deficiency. ***Methods:*** We examined 23 children treated with hGH (24 U/m^2/week) during a median of 4 (range 1.5–5.5) years; group 1: 10 young underweight (age 0.3–4.1 years), group 2: 8 prepubertal overweight (age 3.7–9.5 years) and group 3: 5 pubertal overweight children (age 9.0–14.6 years). ***Results:*** After 4 years of therapy, height gain amounted to 1.8 SD; height (0.0 SD) and hand length (–0.2 SD) were normalised in the 2 prepubertal groups; in children above 6 years, height prediction approached parental target height. Weight for height rose in group 1 (to 0.64 SD) and decreased in group 2 (to 0.71 SD) to normal levels. Bone maturation of the pubertal children was too advanced to show a clear growth response to GH (height gain 0.42 SD). Even in this group, weight for height was reduced, but remained supernormal. ***Conclusion:*** Under exogenous GH, growth and body proportions are normalised in prepubertal children. With early institution of treatment, final height prediction reaches the parental target height range after 3 years. Such a growth-promoting effect of exogenous GH has so far only been described in children with GH deficiency.

Introduction

The Prader-Labhart-Willi syndrome (PWS), at present the most frequent monogenetic form of obesity, is further characterised by polyphagia, muscle hypotonia, mental retardation, short stature and hypogonadism. Despite

This work is dedicated to our teacher, Prof. Andrea Prader, who helped us to initiate this study and supported and motivated us with great commitment.

Supported by the Swiss National Science Foundation grant 32.056063.98 and the Swiss Academy of Medical Science grant NF 455/98.

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profound knowledge on the genetic condition in PWS, the link to symptomatology is only poorly understood. There is evidence that various hypothalamic centres are involved, but to date, gonadotropin deficiency is the only clearly documented endocrine hypothalamic disorder [1]. Several lines of evidence suggest, however, that a growth hormone (GH) deficiency (GHD) due to hypothalamic dysregulation may contribute to an abnormal growth pattern, decreased lean body mass and increased body fat [2–4].

In children with PWS, GH secretion was shown to be decreased [5, 6]. As similar results were found in simple obesity [6, 7], a controversy arose as to whether insufficient GH secretion is the consequence of obesity, or whether there is genuine GHD due to a hypothalamic dysfunction. In contrast to simple obesity [6, 8], however, children with PWS are short for age [9], the average height of PWS males being reported as 160.6 cm (–2.4 SD) and females as 150.2 cm (–2.5 SD) [9]. In addition, insulin-like growth factor (IGF)-I levels as well as insulin secretion [6, 10] and lean body mass are decreased [11], as is the case in GHD. Because IGF-I levels are not as low as expected in GHD, it was hypothesised that hyperalimentation [12] could partly counteract the effect of hypothalamic GHD and lead to relatively higher IGF-I levels [5, 6, 10, 13].

Based on the assumed hypothalamic GHD, children with PWS were treated with GH, even though short stature is not their major complaint. The purpose of GH therapy was to diminish body fat and to increase muscle mass, as demonstrated in children with GHD under substitution [14, 15]. One to two years of therapy in children with PWS have been shown to improve height [16], body composition [5, 6, 13, 17] and the patients' general well-being [13].

In the present article, we analyse the growth response to exogenous GH in these children in three respects: (1) do the growth-promoting effects vary depending on the different phases of clinical presentation; (2) does long-term GH therapy normalise height, hand and foot length and also prediction of adult height, or is diminished growth directly related to the genetic defect, and (3) do growth dynamics, triggered by GH, further elucidate the assumed yet controversial hypothalamic GHD?

Patients and Methods

Twenty-three children with PWS, documented by deletion or uniparental disomy of chromosome 15, were studied. As proposed by others [18], the children were divided into 3 groups (table 1) based on the age-related variations in the syndrome's manifestations, whereby group 1 consisted of the young, still underweight children (weight for height (WfH) SDS < 0), group 2 of the prepubertal overweight children (WfH SDS > 0), and group 3 of the pubertal overweight children (breast stages 2 or 3, according to Tanner, or testicular volume above 3 ml, and pubertal bone age of ≥ 11 years in girls and ≥ 13 years in boys). The pubertal group included 2 rather young girls with early spontaneous puberty, who fulfilled all the criteria of puberty stated above. In some adolescents with PWS, normal or even precocious onset of pubertal development has been described before [19].

The children were treated with 24 IU/m^2/week (~ 0.037 mg/kg/day) recombinant human GH (Pharmacia & Upjohn, Dübendorf, Switzerland), administered in daily subcutaneous injections during 4 (range 1.5–5.5) years. As IGF-I levels were elevated under this regime [13], the children under 2 years of age (8 of group 1) were started on a lower dose (18 IU/m^2/week, ~ 0.025 mg/kg/day). The study was approved by the Ethics Committee of the Children's University Hospital of Zurich and informed consent was obtained from the parents.

No additional medication was administered besides sex steroids in 3 pubertal patients with hypogonadism after the age of 14.5 years and after 18 months of GH therapy as well as 50 μg *L*-thyroxine for hypothalamic hypothyroidism in 1 boy (table 1).

All anthropometric measurements were performed every 6 months by the first author according to standard techniques [20] and are given as SDS using the First Zurich Longitudinal Study [20] as reference, with the exception of arm span, hand and foot length, for which the standards of the Oosterwolde study [21] were chosen. The first growth velocity value in the very young children (table 1; patients 1–6 of group 1) was calculated with measurements provided by the birth clinic or the general practitioner and therefore was not included in the evaluation.

The cumulative height gain was defined as the difference between the height of each patient at the end of the observation period minus height at the beginning of GH therapy, both expressed as the standard deviation score (SDS).

Bone age (BA) was determined every 12 months after the 1st year of life according to Greulich and Pyle [22]. The progress of skeletal maturation was assessed by the ratio of BA to chronological age (CA), which, as a rule, should be 1 in normally growing children [22]. In children with a BA of >6 years (n = 17, 4 children of group 1 and all children of groups 2 and 3), the final height prediction was calculated using the radius, ulna, short bones method of Tanner et al. [23] (RUS/TW2) as well as that of Bayley and Pinneau [24], and compared to the parental target height. We gave preference to the presentation of the results based on the TW2 method, because this method has been shown to be the most accurate in children with normal growth potential [25].

Taking into account abnormal body composition and reduced height of untreated children with PWS, we believe that WfH is the most adequate representation of weight changes induced by GH therapy, since height is expected to increase under GH. An analysis of body composition is presented elsewhere [26]

Metabolic Follow-Ups

Before therapy and at intervals of 6–12 months during therapy, blood samples were taken between 8 and 9 a.m. after a 12-hour overnight fast. Glucose and HbA1c were monitored by standard methods (hexokinase method and immunological quantification, respectively, Roche, Rotkreuz, Switzerland).

Table 1. Clinical data of the children with PWS at the beginning of therapy

Child No.	Sex	Age, years	Bone age Greulich-Pyle, years	Height, SDS	Weight for height, SDS	Parental target height, SDS	Study period, months
Group 1: young underweight children (n = 10; 3f, 7m)							
1	m	0.30	n.d.	–0.83	–0.91	0.92	36
2	m	0.50	n.d.	–1.90	–1.82	1.49	42
3	f	1.10	0.50	–1.80	–2.23	1.30	42
4	f	0.80	n.d.	–0.88	–2.01	1.11	48
5	f	1.00	0.25	–4.90	–3.04	–0.02	48
6	m	0.60	0.50	–1.80	–1.77	0.35	54
7[1]	m	1.50	0.75	–1.52	–2.47	–1.73	54
8	m	1.80	1.25	–1.60	–0.64	0.83	60
9	m	3.00	2.00	–1.88	–1.24	0.92	48
10	m	4.10	2.00	–3.90	–2.78	–0.21	66
	Median	*1.05*	*0.75*	*–1.80*	*–1.91*	*0.87*	*48*
	Range	0.30–4.10	0.25–2.00	–4.9 to –0.83	–3.04 to –0.64	–1.73–1.49	36–66
Group 2: prepubertal overweight children (n = 8; 4f, 4m)							
11	f	3.70	2.25	–1.90	4.14	1.49	60
12	m	6.70	6.25	–0.60	3.00	0.54	30
13	f	5.00	4.25	–0.80	3.16	–0.35	60
14	f	6.80	6.50	–2.08	6.38	–0.35	60
15	m	6.80	5.00	–1.40	4.37	1.30	60
16	m	7.00	7.75	–1.60	4.34	–0.02	60
17	f	7.10	5.75	–2.43	0.84	0.26	60
18	m	9.50	9.50	–2.10	3.76	–0.40	48
	Median	*6.80*	*6.00*	*–1.75*	*3.95*	*0.12*	*60*
	Range	3.70–9.50	2.25–9.50	–2.43 to –0.6	0.84–6.38	–0.4–1.49	30–60
Group 3: pubertal overweight children (n = 5, 4f, 1m)							
19	f	11.10	11.00	–0.40	5.31	1.11	30
20	f	9.00	11.50	0.10	6.29	1.58	18
21[2]	f	13.30	13.00	–4.31	4.31	–0.78	48
22[3]	m	13.50	14.75	–0.74	12.04	0.07	54
23[4]	f	14.60	12.50	–4.82	1.57	–0.91	48
	Median	*13.30*	*12.50*	*–0.74*	*5.31*	*0.07*	*48*
	Range	9.0–14.6	11.0–14.8	–4.82–0.1	1.57–12.04	–0.91–1.58	18–54

[1] Substitution with *L*-thyroxine 50 µg/day.
[2] Substitution with ethinylestradiol since 14.5 years of age.
[3] Substitution with testosterone 100 mg i.m. since 14.8 years of age.
[4] Substitution with a combination of estradiol/progesterone since 16.6 years of age.

Statistical Methods

As several parameters show a skewed distribution, all values are depicted as medians and ranges. The changes induced by GH therapy after 6, 24, 36, 48 and 60 months were tested by the nonparametric Wilcoxon signed ranks test for paired samples, and p values of <0.05 were considered significant. All data were processed by GAS 3.3 of the Institute for Medical Informatics (IMI, Zurich, Switzerland).

Results

Height before therapy was reduced to below the normal mean in all but 1 patient (No. 20, 0.1 SD); no statistically significant difference was found between groups 1 and 2. In the prepubertal children (groups 1 and 2) height rose significantly under GH therapy (fig. 1a, 2a) up to a normal average after 3 years. During the first 6 months,

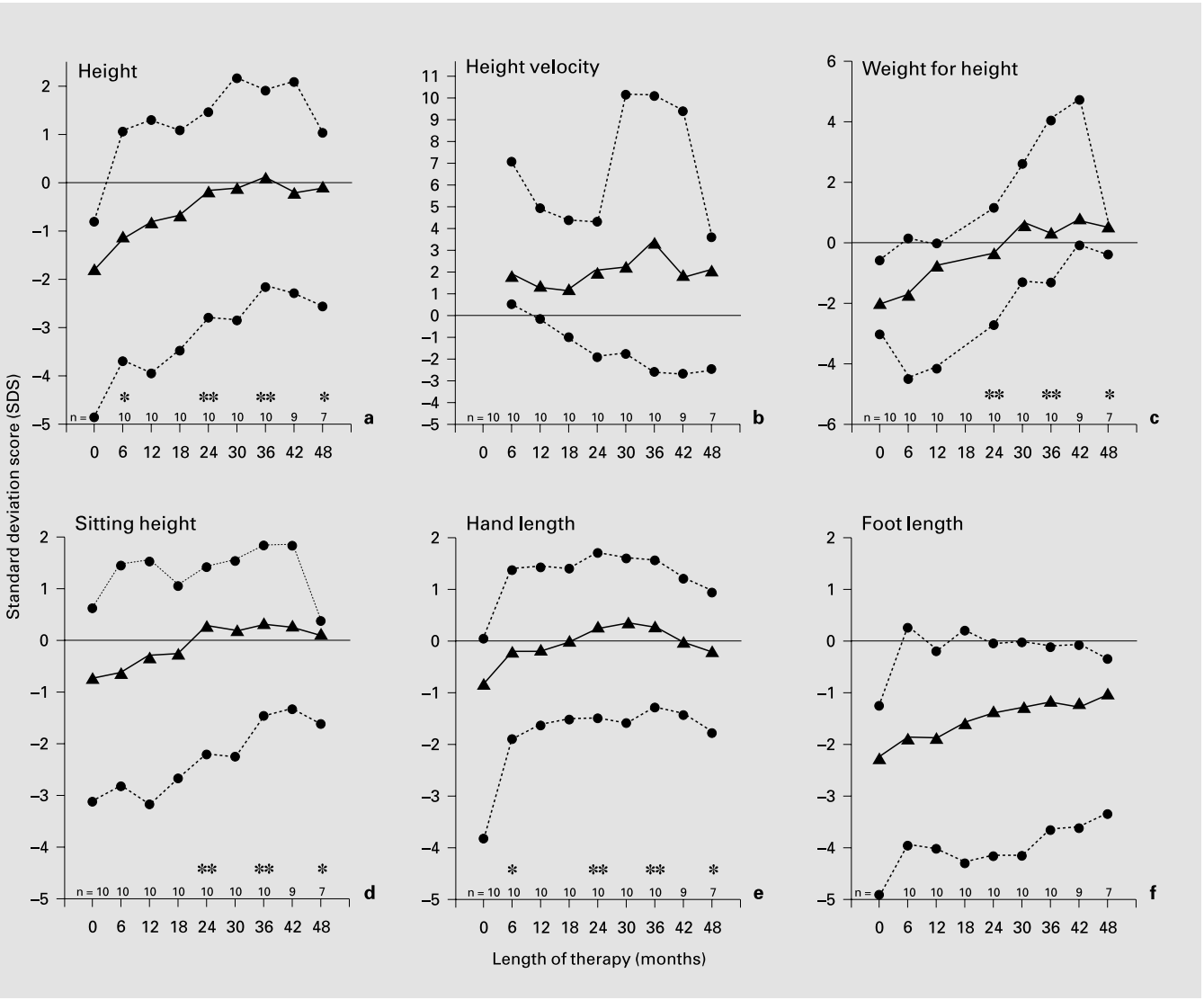

Fig. 1. Young underweight children with PWS (group 1, ▲) before and during 4 years of GH therapy, as medians (solid lines) and ranges (broken lines). Significant differences versus 0 months are indicated at 6, 24, 48 and 60 months as: * $p < 0.05$; ** $p < 0.01$.

height velocity dramatically increased in all patients of group 2 and remained above 2 SD throughout 3 years of therapy (fig. 2b). In the young underweight children (group 1), the increase in growth velocity during therapy could not be ascertained statistically, firstly, because the growth velocity SDS before therapy was not included in the evaluation, and secondly, because only 3 children, those more than 18 months of age (No. 8–10; table 1), showed a clear peak (>4 SDS) immediately after institution of GH therapy. In the 7 youngest children (≤18 months at start), growth velocity only peaked when normal weight (WfH ≥0) was reached; this occurred on average after 24 months of treatment (fig. 1c), and is reflected by a peak of height velocity at 36 months (fig. 1b). Nevertheless, height gain in group 1 (fig. 1a) during each 6-month period, as well as the cumulative height gain after 48 months (median 2.1 SD, range 0.6–2.7) did not differ statistically from group 2 (1.6 SD, range 0.7–2.5).

The initial BA (table 1) was retarded in group 1 (median ratio BA/CA 0.5, range 0.3–0.8), but only moderately in group 2 (BA/CA 0.9, range 0.6–1.1). During therapy, BA approached the CA (BA/CA = 1.0) without further

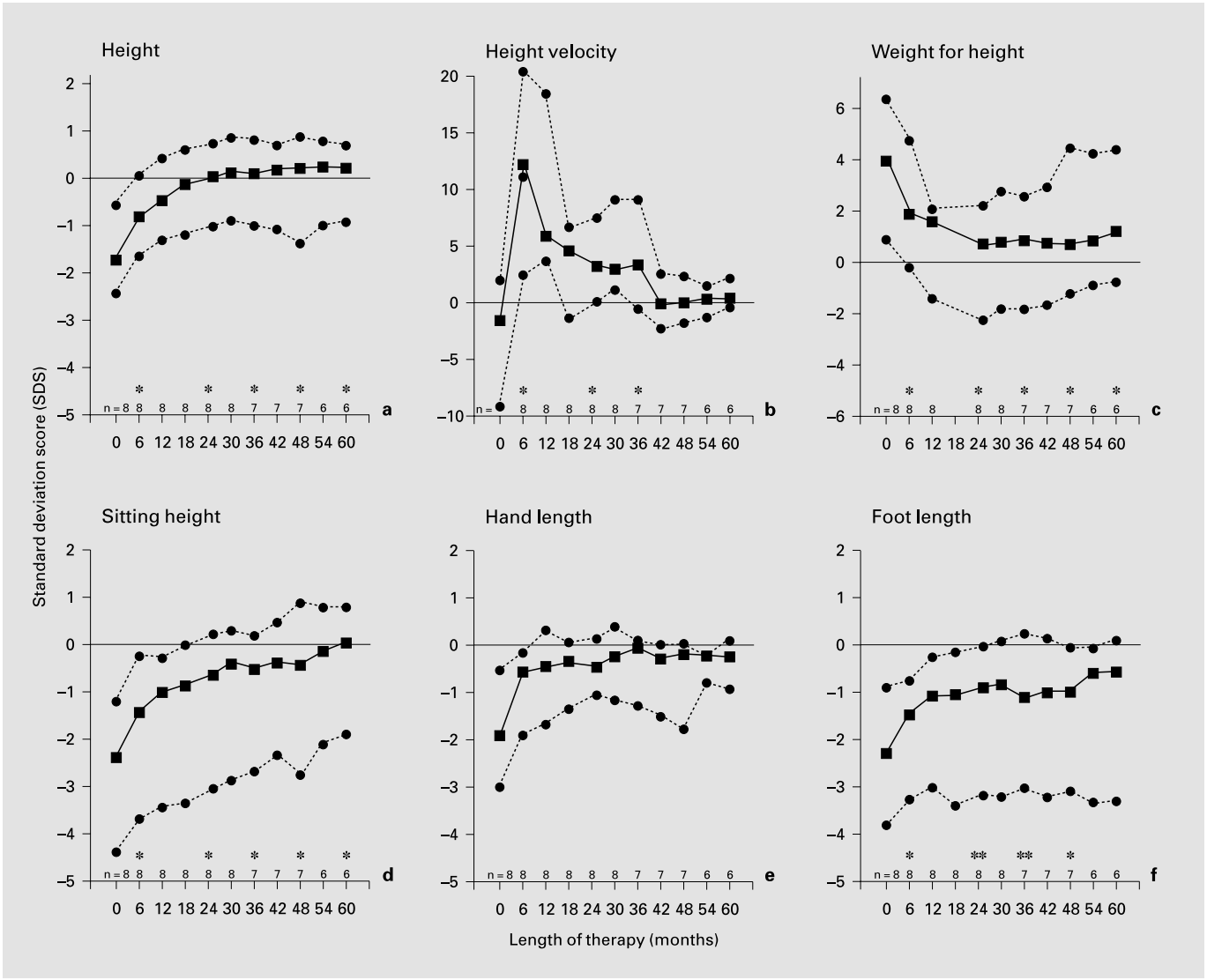

Fig. 2. Prepubertal overweight children with PWS (group 2, ■) before and during therapy with GH. Symbols as in figure 1.

acceleration, in group 2 earlier than in group 1, at 12 and 48 months, respectively. The prediction of final height (combined groups, cf. Methods) improved during therapy, and the gap between predicted and parental target height decreased up to 60 months, either calculated by the TW2 method (from −9.0 to 2.6 cm difference between predicted and target height, fig. 3), or by the Bayley and Pinneau [24] method (from −10.4 to 0.6 cm difference between predicted and target height). The increase in TW2 height prediction was still significant at 48 months, when young or pubertal patients with a short observation period (<3 years) were eliminated. There was not a single child of the 17 in whom TW2 height prognosis clearly deteriorated under GH therapy.

The changes in sitting height entirely reflected those of height in groups 1 and 2 (fig. 1d, 2d). Hand and foot length before therapy was below the normal mean in all patients. The increase in hand and foot length, expressed in SDS, was similar to height increase in all groups, with the same initial growth spurt in group 2 (fig. 1e, f; 2e, f). Hand length was less reduced than foot length in all groups at all times.

WfH in group 1 was reduced before therapy (fig. 1c) and continuously increased up to 36 months into treatment. In contrast, in group 2 (fig. 2c), of which all children were overweight by definition, WfH dropped during the first 2 years of GH therapy, the decrease in WfH being greatest during the first 6 months of therapy; after 2 years WfH stabilised on the same level.

The anthropometric data of the pubertal patients (group 3) greatly varied, both before and during therapy, depending on their age. At the beginning, height and bone age were less reduced than in prepubertal children with PWS (table 1). Height courses were heterogeneous under therapy, the 2 young pubertal girls showing a better response to GH (fig. 4a); the findings for sitting height, hand length and foot length were similar to height (data not shown). Height velocity (fig. 4b) increased during the first 6 months of therapy (from a median of –0.26 to 2.7 SD). WfH SDS (fig. 4c) decreased in 4 of the 5 patients during GH therapy, these 4 being the more obese ones.

Carbohydrate Metabolism

Fasting glucose levels significantly increased during the first year of therapy (median from 4.1 to 4.4, ranges 3.4–4.6 and 3.7–4.6 mmol/l, respectively, $p < 0.05$), but remained entirely within the normal range. HbA1c levels were also normal under GH therapy.

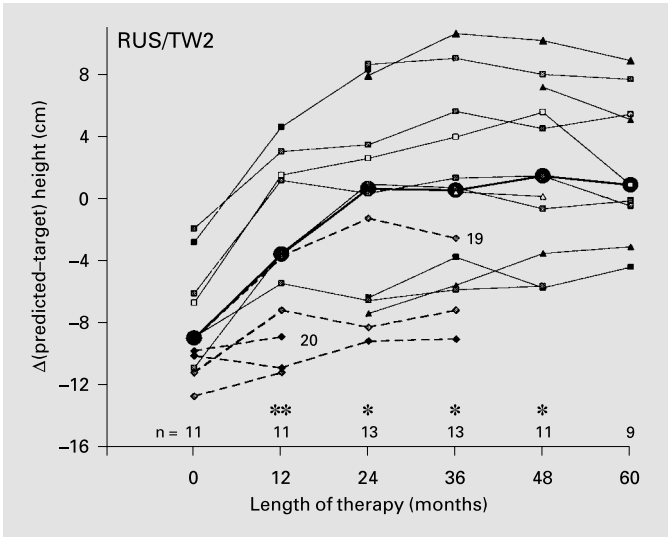

Fig. 3. Prediction of final height for PWS patients during GH therapy. Differences between predicted minus target height (cm) in 17 patients of all groups (see Methods), as median (solid heavy line) and individual graphs of prepubertal (■ ▲, fine lines) or pubertal (◆, broken lines) patients. Levels of significance as indicated in figure 1.

Discussion

The presented clinical data on spontaneous growth in children with PWS before treatment are as conflicting as the reported biochemical results [6, 10]: while the observed reduced height for parental height and short hands and feet are features of PWS [9, 27] supporting the assumption of an underlying GH deficiency, normal growth velocity and lack of skeletal retardation are arguments against GHD in PWS. It has been shown, however, that there is insufficient growth velocity and height loss in children with PWS in the underweight period during the first years of life. Only after age 3, when obesity sets in, growth velocity turns normal [9]. Since healthy obese children are taller than normal-weight children between the ages of 4 and 10 years and their bone maturation is accelerated [8], we suggest that growth in PWS represents a combination of two different patterns: the acceleration induced by marked obesity may counteract growth retardation of GHD.

Based on this hypothesis, we analysed the influence of exogenous GH on growth dynamics in children with PWS to provide further arguments for the assumed GHD in this form of syndromal obesity. The dramatic increase in height velocity and its long-standing elevation as well as the overall height gain under GH therapy observed in the prepubertal obese children of this study resembled the catch-up growth encountered in GHD during substitution with GH [28, 29]. The growth velocity of the children with PWS during GH therapy distinctively exceeded that reported in short-statured patients without GHD even under higher GH doses [30, 31]. In infants, the growth pattern is less dependent on GH alone, but mainly influenced by perinatal factors or food supply [32]. This was reflected in our group-1 patients by the individual timing of peak growth velocity, occurring immediately after onset of GH therapy in the older, and only after normalisation of body weight in the infants less than 18 months old. Therefore, height velocity SDS in the young underweight PWS subjects as a group was not suited to reflect the efficacy of GH treatment. In this group, as well as in other studies in young children with GHD [33–35], the GH effect was more appropriately reflected by height gain, which, in our study, was equivalent to that of the prepubertal overweight group, and continued to increase during the 4th year of GH treatment. As the increase in hand and foot length was similar to the height increase in all groups, the prepubertal children over 3 years of age no

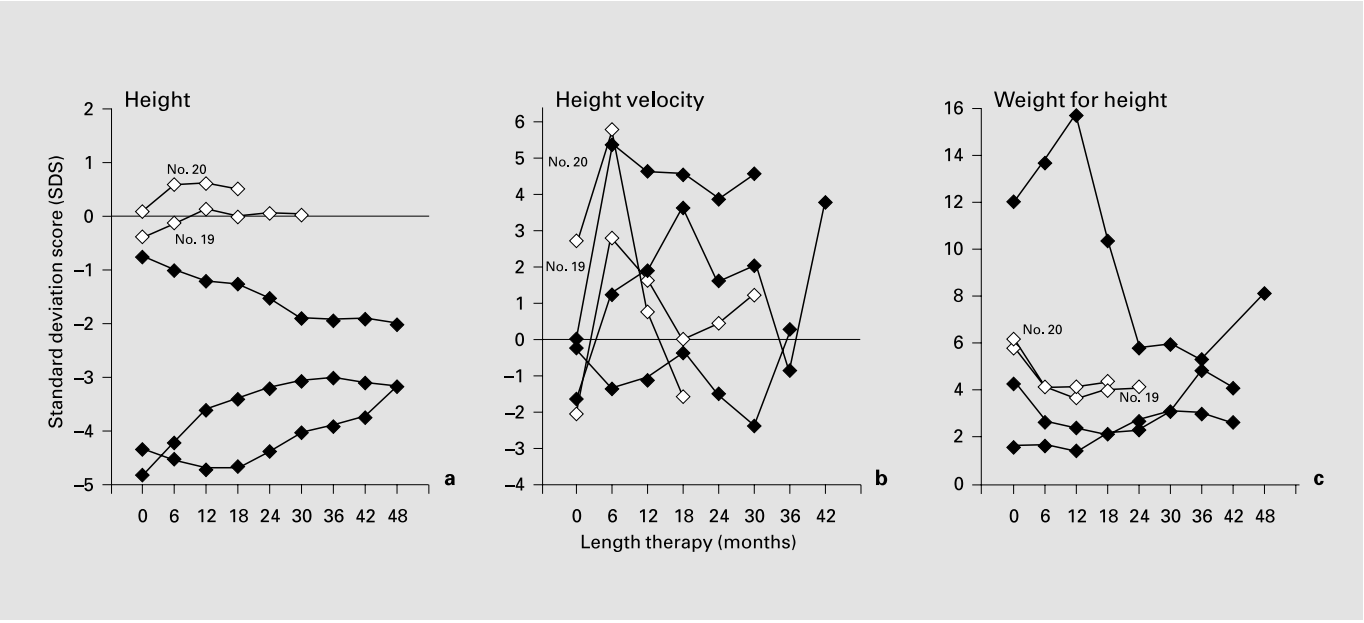

Fig. 4. Individual graphs for height (**a**), height velocity (**b**) and weight for height (**c**) of the 5 pubertal patients (group 3).

longer had small hands and feet and all body proportion parameters were balanced, as known in GHD patients during therapy [36].

Prediction of adult height, assessed by two different methods, considerably improved in the prepubertal children and reached the range of their parental target height. Before final height has been achieved, however, no definite statements can be given. Even though BA was not clearly retarded before therapy, a considerable height gain was observed, confirming that BA maturation before therapy in prepubertal children is not a reliable predictor of the growth response to GH, as recently shown in GHD [37]. In pubertal patients, prediction of final height remained clearly below their target height, as was expected; for various reasons, e.g. advanced bone maturation and gonadotropin deficiency, growth potential was limited.

In contrast to the continuous height gain throughout GH therapy, WfH changed only during the first 2 years of treatment in prepubertal patients. This suggests that the metabolic effects of GH might be of shorter duration than the growth anabolic effects, or that they are counteracted by the normal age-dependent increase in fat mass [15], as has also been shown earlier in GHD [14, 15].

In summary, under exogenous GH, growth and body proportions in prepubertal children with PWS are normalised. If treatment is instituted early enough, final height prediction will reach the parental target height range after 3 years, and short stature as well as small hands and feet will no longer be present. A growth-promoting effect of exogenous GH of this order has so far only been described in children with GHD. We therefore conclude that the diagnosis of GHD in PWS might be hindered by the coinciding obesity. The speculation that short stature and small hands and feet are rather related to insufficient GH secretion than directly to the genetic defect, will have to be confirmed by a normal final height in treated children with PWS. Although short stature is not the main complaint of these children and their families, these results illustrate the efficacy of GH treatment in patients with PWS.

Acknowledgements

The authors thank Mrs. Claudia Weinmann for research coordination and technical assistance, and Prof. Theo Gasser (Department of Biostatistics, Institute of Social and Preventive Medicine, University of Zurich), as well as Luciano Molinari, PhD (Pediatric Department, University Hospital, Zurich), for their valuable criticism, and Mrs. Karin Stutz for her help in translating and preparing the manuscript. Our special thanks go to the PWS Association of Switzerland and the parents and their PWS children for their great commitment and efforts.

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