Growth Hormone Treatment in Children With Prader-Willi Syndrome: Three Years of Longitudinal Data in Prepubertal Children and Adult Height Data From the KIGS Database

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Context: Longitudinal data of children with Prader-Willi syndrome (PWS) treated with genotropin were registered in the Pfizer International Growth Database (KIGS).

Objective: To evaluate efficacy and safety of growth hormone (GH) treatment in a large group of children with PWS.

Design: Data registered in KIGS from 1987 to 2012.

Setting: Worldwide retrospective cohort study.

Patients: Patients included 522 prepubertal children treated with GH for three years and 173 children who had reached adult height. Safety analysis included 2332 children. Intervention involved GH treatment.

Main outcome measure: Height standard deviation score (SDS), body mass index (BMI) SDS, occurrence of serious adverse events, and deaths reported in KIGS.

Results: In prepubertal children, mean (standard deviation) height SDS improved to −0.31 (1.34) ($P < 0.05$) during three years of GH treatment. In the adolescent group, height SDS improved until the start of puberty to −0.22 (1.31) ($P < 0.05$) but had a loss of −0.77 (0.81) during puberty, resulting in a mean adult height SDS of −1.19 (1.37). Total height gain was 0.95 (1.32) SDS. BMI SDS increased in the prepubertal group from 1.11 (2.09) to 1.53 (1.43) ($P < 0.05$) and did not significantly change in the adolescent group, who had a BMI SDS at an adult height of 1.78 (1.26). KIGS contained 12 death reports.

Conclusions: GH treatment in children with PWS significantly improves linear growth. BMI remains on average below +2 SDS, in contrast to the natural course of increasing obesity in PWS. Safety should be closely monitored in children with PWS, with and without GH treatment. (***J Clin Endocrinol Metab*** **102: 1702–1711, 2017)**

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder. PWS arises from a lack of expression of paternally inherited genes on chromosome 15q11-q13, caused by deletion, maternal uniparental disomy, imprinting center defect, or balanced translocation (1). According to European surveys, the incidence of the disease is estimated at around 1 in every 15,000 to 30,000 births, affecting boys and girls equally

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Abbreviations: AE, adverse event; BMI, body mass index; DM, diabetes mellitus; GH, growth hormone; Ht-MPH, height to midparental height; IGF-I, insulin-like growth factor 1; KIGS, Pfizer International Growth Database; PWS, Prader-Willi syndrome; SAE, serious adverse event; SD, standard deviation; SDS, standard deviation score.

(2, 3). Children with PWS are characterized by short stature for genetic background, muscle hypotonia, hyperphagia, obesity, hypogonadism, behavioral problems, and developmental delay (4, 5). Most of the characteristic features of PWS are thought to be the result of hypothalamic dysfunction (6).

Children with PWS have impaired growth, most likely caused by a combination of a growth hormone (GH)/insulin-like growth factor 1 (IGF-1) deficiency and a lack of pubertal growth spurt (7, 8). GH treatment is approved for children with PWS and has been shown to improve growth and body composition (9–13). In addition, GH treatment has beneficial effects on mental and motor functions (9, 14, 15), exercise capacity (16), sleep-related cardiorespiratory control (17), and surgical risks (18). Contrasting with these benefits, sudden death in GH-treated children with PWS has been reported (19, 20). The most common cause of death in children with PWS is a respiratory infection in both GH-treated and untreated children (19). Underlying predisposing causes include sleep apnea (5), tonsillar and adenoid hypertrophy (19), central adrenal insufficiency (21), or a combination (22).

However, long-term data of a large group of GH-treated prepubertal children with PWS have not been reported. Results of nationwide studies from the United States, the Netherlands, and Switzerland are reassuring (23–25) but have the limitation of small patient numbers because PWS is a rare syndrome. Therefore, the current study was undertaken to evaluate growth during three years of GH treatment and adult height data in a large group of children with PWS by using the Pfizer International Growth Database (KIGS), containing data from 1987 to 2012. We hypothesized that GH treatment of three years would significantly improve height standard deviation score (SDS) and body mass index (BMI) SDS in prepubertal children with PWS compared with baseline and that GH treatment would normalize adult height SDS in adolescents with PWS who started GH treatment at least two years before entering puberty. In addition, we expected to find no increased mortality compared with the reported mortality risk of 3% per year in a population of non-GH-treated patients with PWS (26).

Patients and Methods

Patients

Patients were selected from the KIGS database, from the start of KIGS in 1987 to 2012, a large international pharmacoepidemiological database with data of children treated with recombinant human GH (Genotropin; Pfizer Inc., New York, NY). The KIGS database consists of patient data that were collected by the physician-investigator during a normal daily clinical practice setting and at the discretion of the treating physician. Patient data were routinely quality controlled by KIGS data monitors.

The first group consisted of prepubertal children with PWS who received GH treatment before puberty for a minimum of three consecutive years. The children remained prepubertal, defined by testicular volume less than 4 mL in boys (27) and breast Tanner stage 1 in girls (28). The second group consisted of adolescents with PWS who started GH treatment at least two years before the onset of puberty and were treated with GH during puberty until near adult height. Adult height or near-adult height was defined as height velocity <2 cm/y at an appropriate chronological age. The third group consisted of all patients with PWS registered in KIGS.

Height, weight, and BMI SDS were determined from the longitudinal growth standards (29, 30) and height and BMI PWS SDS from the growth standards for untreated children with PWS (31). Height to midparental height (Ht-MPH) was calculated to indicate the adjusted parental height. Bone ages, based on the method of Greulich and Pyle (32), were taken as reported by the treating physician.

At the time of the KIGS founding in 1987, enrollment was independent from informed consent in many countries, but since 2002, patients were enrolled only after informed consent of parents had been obtained by the local physician. KIGS was conducted in accordance with the Declaration of Helsinki (33).

Design

The primary aim of this study was to evaluate prepubertal growth during three years of GH treatment and to evaluate near-adult height data after GH treatment in a large group of children with PWS enrolled in KIGS. The secondary aim of this study was to evaluate safety during GH treatment of all children with PWS enrolled in KIGS.

The diagnosis of PWS in KIGS was based on genetic testing or consensus diagnostic criteria and reported to KIGS as code 3.2.3 (PWS without chromosomal aberration) or 3.3.5 (PWS with chromosomal aberration).

Adverse events and serious adverse events

An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject following administration of a Pfizer product or use of a Pfizer medical device. The definition of a serious adverse event (SAE) was any adverse event, without regard to causality, that 1) resulted in death or was life threatening (immediate risk of death), 2) required inpatient hospitalization or prolongation of existing hospitalization, 3) resulted in persistent or substantial disability or incapacity, or 4) resulted in congenital anomaly or birth defect.

The database protocol required that physicians reported all adverse events of patients followed in KIGS, regardless of whether they were associated with GH treatment.

Statistical methods

Data are presented as mean with standard deviation (SD) or number (%) for chosen variables at given time points. Differences between groups were tested with a t test when the distribution was normal and Wilcoxon rank-sum test otherwise. For the prepubertal analysis, the primary comparison was height SDS after three years of GH treatment vs height SDS at

the start of GH treatment. For the near-adult height analysis, the primary comparison was height SDS at near-adult height vs height SDS at the start of GH treatment.

Multiple linear regression analyses were calculated, with the change in height SDS between near-adult height and start of GH treatment as the dependent variable. The independent variables were age, height SDS, and BMI SDS at the start of GH treatment, midparental height SDS, sex, and mean total GH dose. *P* values <0.05 were considered significant. To simplify Tables 2 and 3, one decimal point was used. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Baseline prepubertal group

Demographic data of the study population, including baseline data of 522 (54.8% boys, 45.2% girls) prepubertal children who received GH treatment for 3 consecutive years, are shown in Table 1. Mean (SD) birth weight and birth length were low [−1.22 (1.16) SDS and −0.28 (1.46) SDS, respectively] but within the normal range (34). Mean (SD) gestational age was 38.4 (2.7) weeks. The diagnosis of PWS was confirmed by genetic studies in 79% of children (413/522). The mean (SD) midparental height SDS was −0.05 (1.14). Prior to the start of GH treatment, 150 children underwent a GH stimulation test with a mean (SD) GH peak of 7.9 (8.9) μg/L and 219 children had serum IGF-1 SDS values [−1.06 (1.52)].

GH treatment was initiated at a mean (SD) age of 4.4 (2.9) years at a dose of 0.23 (0.07) mg/kg/wk. Mean (SD) baseline height SDS was −2.05 (1.46), weight SDS was −0.23 (2.12), and BMI SDS was 1.11 (2.09). Mean (SD) baseline height velocity was 7.2 (4.2) cm/y. Bone age data were available in around 21% (111/522) of the children. At the time of starting treatment, mean (SD) bone age was 4.3 (3.1) years. At GH start, bone age was delayed in 81% (90/111) of the children, and in 50% (56/111), this delay was by more than one year.

Baseline adolescent group

Baseline data of 173 adolescents (46.8% boys, 53.2% girls) with PWS who reached near-adult height and received GH treatment since at least two years before entering puberty are shown in Table 1. Mean (SD) birth weight and birth length were low [−1.35 (0.99) SDS and −0.29 (1.10) SDS, respectively] but within the normal range (34). The diagnosis of PWS was confirmed by genetic studies in 79% of children (137/173). Mean (SD) gestational age was 38.6 (3.0) weeks. Mean (SD) midparental height SDS was −0.07 (1.20). Prior to the start of GH, 69 children underwent a GH stimulation test with a mean (SD) GH peak of 8.7 (7.7) μg/L, and serum IGF-1 SDS values were −1.69 (1.25).

GH treatment was initiated at a mean (SD) age of 8.2 (2.7) years at a dose of 0.22 (0.07) mg/kg/wk. Mean (SD) baseline height SDS was −2.14 (1.40), weight SDS was

Table 1. Baseline Characteristics

Characteristic	Prepubertal Group	Adolescent Group	All
Male/female	522 (55/45)	173 (47/53)	2332 (51/49)
With genetic aberration	413/522 (79)	137/173 (79)	1853/2332 (79)
Deletion	182/295 (62)	38/79 (48)	718/1197 (60)
mUPD	65/295 (22)	25/79 (32)	263/1197 (22)
Methylation imprinting	6/295 (2)	0/79 (0)	41/1197 (3)
Unknown	42/295 (14)	16/79 (20)	175/1197 (15)
Age, y	4.36 ± 2.88	8.18 ± 2.68	6.0 ± 4.33
Birth weight SDS	−1.22 ± 1.16	−1.35 ± 0.99	−1.26 ± 1.21
Birth length SDS	−0.28 ± 1.46	−0.29 ± 1.10	−0.36 ± 1.41
Gestational age, wk	38.4 ± 2.7	38.6 ± 3.0	38.3 ± 2.9
Midparental height SDS[a]	−0.05 ± 1.14	−0.07 ± 1.20	−0.12 ± 1.17
Maximum GH peak, μg/L	7.94 ± 8.94	8.65 ± 7.67	7.55 ± 7.35
IGF-1 SDS	−1.06 ± 1.52	−1.69 ± 1.25	−1.09 ± 1.78
Height SDS[a]	−2.05 ± 1.46	−2.14 ± 1.40	−1.90 ± 1.50
Height SDS PWS	−0.13 ± 0.95	−0.50 ± 1.03	−0.06 ± 1.04
HV, cm/y	7.16 ± 4.21	5.21 ± 2.30	6.55 ± 4.03
Weight SDS[b]	−0.23 ± 2.12	0.41 ± 1.65	0.20 ± 2.22
BMI SDS[b]	1.11 ± 2.09	1.85 ± 1.27	1.41 ± 2.11
BMI SDS PWS	0.05 ± 1.06	−0.19 ± 1.01	0.17 ± 1.10
Bone age, y	4.32 ± 3.07	6.77 ± 3.17	6.39 ± 4.37
GH dose, mg/kg/wk	0.23 ± 0.07	0.22 ± 0.07	0.23 ± 0.08

Data are expressed as number (%) or mean ± SD.

Abbreviations: HV, height velocity; mUPD, maternal uniparental disomy.

[a] According to age- and sex-matched reference values (29).

[b] According to age- and sex-matched reference values (30).

0.41 (1.65), and height velocity was 5.21 (2.30) cm/y. Bone age data were available in 36% (63/173) of the children. At the time of starting treatment, mean (SD) bone age was 6.8 (3.2) years. Bone age was delayed in 76% (48/63) of the children, and in 54% (34/63), this delay was by more than one year.

Three years of GH treatment in prepubertal children

Table 2 shows the growth data during three years of GH treatment in 522 prepubertal children. After one year of treatment, mean (SD) height had improved from −2.05 (1.46) SDS to −1.04 (1.40) SDS ($P < 0.05$), and after three years, height had completely normalized to −0.31 (1.34) SDS ($P < 0.05$, compared with baseline). Mean (SD) height velocity increased during the first year of GH treatment from 7.16 (4.21) to 11.27 (3.11) cm/y. In the subsequent two years, mean (SD) height velocity gradually decreased to 8.37 (2.09) and 7.32 (1.84) cm/y, respectively. In accordance with height SDS, Ht-MPH SDS had also normalized after three years of GH treatment. Mean (SD) BMI SDS increased according to age-matched reference data from 1.11 (2.09) to 1.53 (1.43) ($P < 0.05$, compared with baseline) after three years of GH treatment.

During three years of GH treatment, mean (SD) bone age delay decreased from 0.94 (1.62) to −0.12 (1.54) years ($P < 0.05$, compared with baseline), indicating that bone age progressed faster than calendar age. Mean GH dose was 0.22 mg/kg/wk during the three years of treatment.

GH treatment until adult height

Table 3 shows the growth data during a mean (SD) of 8.7 (2.7) years of GH treatment in 173 adolescents with PWS. After one year of GH treatment, mean (SD) height had improved from −2.14 (1.40) SDS to −1.23 (1.34) SDS ($P < 0.05$), and at the start of puberty, mean (SD) height had normalized to −0.22 (1.31) SDS ($P < 0.05$, compared with baseline). However, mean (SD) delta height SDS declined from the start of puberty to adult height by −0.77 (0.81), resulting in a mean (SD) adult height SDS of −1.19 (1.37), significantly higher than at baseline but also significantly lower than at the start of puberty (both $P < 0.05$). In this international PWS cohort, the mean (SD) near-adult height was 170.1 (9.21) cm in boys and 155.8 (8.0) cm in girls. In accordance with height SDS, mean (SD) Ht-MPH SDS was −1.05 (1.21) at adult height ($P < 0.05$, compared with baseline). BMI SDS did not significantly change during GH treatment and was a mean (SD) of 1.78 (1.26) at adult height. Mean prepubertal dose of GH was 0.22 mg/kg/wk and mean pubertal dose was 0.18 mg/kg/wk, resulting in a mean total dose of 0.19 mg GH/kg/wk during the entire treatment period.

Multiple linear regression analysis

We performed a multiple regression analysis to determine associations between patient characteristics and gain in height SDS from GH start to adult height SDS (Table 4). Height SDS PWS and BMI SDS PWS at GH start were both negatively associated with adult height SDS ($\beta = -0.3$ and $\beta = -0.4$, both $P < 0.01$). Midparental height SDS was positively associated with adult height SDS ($\beta = 0.3$, $P < 0.01$). GH dose (at start in mg/kg/wk) showed a trend toward a positive association with adult height SDS ($\beta = 2.0$, $P = 0.07$). Age at start of GH treatment was not significantly associated with adult height SDS.

AEs

A total number of 1280 AEs and SAEs were reported in 545 of the 2332 patients with PWS with patient records in KIGS (8783 treatment years). Of a total of 545 patients, 174 had SAEs. Table 5 includes AEs that are known to be specific for PWS and GH treatment, as well

Table 2. Growth Data and BMI During 3 Years of GH Treatment in 522 Prepubertal Children With PWS

Characteristic	Baseline	One Year	Two Years	Three Years
Age, y	4.4 (2.9)	5.4 (2.9)	6.4 (2.9)	7.4 (2.9)
Bone age delay[a]	0.9 (1.6)	0.7 (1.3)	0.4 (1.6)	−0.1 (1.5)
Height SDS	−2.1 (1.5)	−1.0 (1.4)	−0.6 (1.4)	−0.3 (1.3)
Height SDS PWS	−0.1 (0.9)	0.5 (1.0)	0.7 (1.0)	0.9 (1.0)
Ht-MPH SDS	−2.0 (1.6)	−1.0 (1.5)	−0.5 (1.5)	−0.2 (1.4)
HV, cm/y	7.2 (4.2)	11.3 (3.1)	8.4 (2.1)	7.3 (1.8)
HV SDS	−1.1 (2.2)	3.6 (3.1)	1.8 (2.3)	1.3 (2.3)
BMI SDS	1.1 (2.1)	1.0 (1.8)	1.4 (1.5)	1.5 (1.4)
Weight SDS	−0.2 (2.1)	0.4 (1.9)	0.8 (1.6)	1.1 (1.5)
BMI SDS PWS	0.1 (1.1)	−0.3 (1.1)	−0.5 (1.7)	−0.4 (1.1)

Data are expressed as mean (SD).

Abbreviation: HV, height velocity.

[a] Chronological age – bone age.

Table 3. Growth Data and BMI Until Adult Height in 173 Adolescents With PWS

Characteristic	Baseline	One Year	Start Puberty	Adult Height
Age, y	8.2 (2.7)	9.1 (2.5)	12.1 (2.3)	17.4 (1.7)
Years of GH			3.7 (2.4)	8.7 (2.7)
Bone age delay[a]	1.2 (1.5)		0.3 (1.5)	
Height SDS	−2.1 (1.4)	−1.2 (1.3)	−0.2 (1.3)	−1.2 (1.4)
Height SDS PWS	−0.5 (1.0)	0.1 (1.1)	0.8 (1.4)	1.6 (1.5)
Ht-MPH SDS	−2.1 (1.4)	−1.1 (1.3)	−0.1 (1.2)	−1.1 (1.2)
HV, cm/y	5.2 (2.3)	9.8 (2.4)		
HV SDS	−1.1 (2.5)	5.5 (3.4)		
Pubertal delta height,[b] cm				17.4 (10.5)
Weight SDS	0.4 (1.7)	0.5 (1.5)	0.8 (1.6)	1.2 (1.6)
BMI SDS	1.9 (1.3)	1.4 (1.3)	1.4 (1.2)	1.8 (1.3)
BMI SDS PWS	−0.2 (1.0)	−0.6 (1.0)	−0.7 (1.0)	−0.6 (1.1)

Data are expressed as mean (SD).

Abbreviation: HV, height velocity.

[a] Chronological age – bone age.

[b] No difference between girls and boys.

as those reported as "serious" and/or "possibly or probably related to GH treatment."

During GH treatment, scoliosis (including surgery) was most frequently reported with 154 cases. Cryptorchidism was reported in 19 boys, and 22 boys underwent orchiectomy/orchidopexy. Sleep apnea syndrome was reported in 53 children of all ages (range, 1.5 to 19.1 years). Before and during GH treatment, psychiatric disorder was reported in 47 children at a mean age of 11 years.

In children with an age range from 8.7 to 14.6 years, four had impaired glucose tolerance, three had hyperglycemia, and three had insulin resistance. Diabetes was reported in 10 children at a mean age of 14.5 years, after a mean GH treatment duration of one year. Three had type 1 diabetes mellitus (DM), and seven had type 2 DM. Two patients with type 2 DM and two with impaired glucose intolerance had the disorder prior to the start of GH treatment. Six patients stopped GH treatment, one stopped and restarted two years later, two continued on the same dose, and one continued on a lower dose.

Papilledema and benign intracranial hypertension were reported in four children within the first four months of GH treatment. Two of the four patients stopped GH treatment. The other two stopped and restarted (one after 4 months the other after 11 months), both with the same dose as before the event. Fractures and joint dislocations were reported in 18 children.

Two cases of leukemia were reported after 0.2 and 3.5 years of GH treatment. Five cases of benign neoplasms were reported. Precocious puberty was reported in five girls and one boy at a mean age of 7.5 years. Six boys developed gynecomastia at a mean age of 12.7 years. Abdominal pain was reported in nine children after a mean duration of 3.1 years of GH treatment.

Infections were frequently reported (n = 55), as well as snoring (n = 20), and 17 children underwent adenoidectomy/adenotonsillectomy. Pneumonia was reported 10 times, tonsillar hypertrophy was noted in 15 children, and obstructive airway disorder occurred in 3 children.

KIGS received 12 death reports (six males) (Table 6). Median (interquartile range) age of death was 10 (2.6 to 15.7) years, and the duration of GH treatment was 1.4 (0.2 to 6.7) years, with a GH dose of 0.20 (0.11 to 0.24) mg/kg/wk. Two patients older than 18 years were not on GH treatment at the time of death and had an unexplained cause of death. The other 10 patients' reported cause of death included gastric perforation, shock followed by disseminated intravascular coagulation, pneumonia (n = 4), bathtub drowning, accident (fall), immunodeficiency, and vomiting and diarrhea followed by a cardiorespiratory arrest.

Postmortem examination was performed in two children, cases 4 and 6, and the cause of death was attributed to pneumonia and respiratory insufficiency. Case 4 presented

Table 4. Multiple Linear Regression Analysis for Gain in Height SDS From GH Start to Adult Height SDS

Characteristic	Regression Coefficient (β)	*P* Value
Age at start GH, y		NS
Sex[a]	0.9	<0.01
Height SDS PWS at start	−0.3	<0.01
Midparental height SDS	0.3	<0.01
BMI SDS PWS at start	−0.4	<0.01
GH dose, mg/kg/wk	2.0	0.07
R^2 statistic	0.43	<0.0001

Abbreviation: NS, not significant.

[a] Girls: reference group.

Table 5. Adverse Events and Serious Adverse Events in 2332 Children With PWS Treated With GH

Characteristic	AEs (SAEs), No.	Age, mean (range), y	Sex	Duration of GH Therapy, y (Minimum–Maximum)	Related to GH Therapy Reported by the Investigator, No.[a]		
					Yes	No	Unknown
Cryptorchidism[b]	19 (5)	5.1 (0.9–17.3)	19 M	1.1 (0.0–6.0)		19	
Orchiectomy/orchidopexy	22	5.1 (2.0–17.4)	22 M	1.7 (0.1–7.2)		20	2
Precocious puberty	6	7.5 (5.2–10.4)	5 F, 1 M	3.0 (1.5–7.1)		4	2
Papilledema/BIH	4 (3)	7.7 (5.6–12.0)	1F, 3 M	0.1 (0.1–0.3)	4		
Abdominal pain	9	10.5 (4.7–13.1)	7 F, 2 M	3.1 (1.1–8.9)		7	2
Intussusception	1 (1)	3.0	1 M	1.3		1	
Peripheral edema	10	13.1 (3.8–16.1)	6 F, 4 M	0.5 (0.1–15.0)	7	2	1
Hypersensitivity	5	11.4 (2.5–12.7)	2 F, 3 M	2.8 (0.4–7.7)		4	1
Pneumonia	10 (10)	5.6 (1.6–11.4)	5 F, 5 M	2.9 (0.1–6.9)		10	
All infections	55	5.4 (0.9–17.2)	29 F, 26 M	1.7 (0.0–7.9)	1	51	3
Fracture	11	13.7 (5.7–18.2)	4 F, 7 M	1.5 (0.3–9.7)		11	
Joint dislocation	7	13.5 (4.4–16.0)	5 F, 2 M	3.2 (0.2–8.0)	1	6	
IGF-1 increased	28	8.3 (2.1–16.6)	14 F, 14 M	3.9 (0.3–8.5)	16	10	2
Diabetes (T1DM, T2DM)	10 (10)	14.5 (10.4–18.5)	4 F, 6 M	1.0 (0.0–6.7)	7	3	
Impaired glucose tolerance	4	9.3 (8.7–11.1)	3 F, 1 M	2.1 (0.6–7.2)	3	1	
Hyperglycemia	3	14.2 (12.5–14.6)	1 F, 2 M	4.1 (0.2–6.5)	2		1
Insulin resistance	3	12.7 (9.8–14.3)	2 F, 1 M	3.1 (2.6–7.5)	1	1	1
Epiphysiolysis	1 (1)	12.6	1 M	0.4		1	
Arthralgia	8	10.6 (4.9–16.2)	4 F, 4 M	1.5 (0.8–3.1)	2	4	2
Kyphosis	14	10.8 (5.6–16.5)	6 F, 8 M	3.9 (1.5–10.4)	2	9	3
Scoliosis[b]	144 (35)	10.2 (0.6–17.5)	84 F, 60 M	1.9 (0.0–9.5)	34	84	26
Scoliosis (including surgery)	154 (45)	10.3 (0.6–17.5)	86 F, 68 M	2.0 (0.0–12.1)	36	91	27
Leukemia	2 (2)	0.9	1 F	0.2		1	
		8.7	1 M	3.5	1		
Benign neoplasms	5 (5)	9.1 (2.8–15.9)	3 F, 2M	3.8 (0.6–7.4)		4	1
Cerebrovascular accident	1	9.5	1 M	1.2		1	
Convulsion/Epilepsy	9 (1)	4.2 (1.3–11.3)	5 F, 4 M	1.6 (0.3–5.3)		8	1
Headache	20	10.9 (4.2–18.1)	7 F, 13 M	1.6 (0.0–7.5)	7	11	2
Psychiatric disorder[b]	47	11.0 (3.4–19.7)	22 F, 25 M	3.4 (0.0–7.4)	3	34	10
Gynecomastia	6	12.7 (9,7–16.3)	6 M	2.5 (1.7–6.8)	1	4	1
Enuresis	11	8.0 (4.3–12.8)	5 F, 6 M	4.0 (0.2–7.9)		11	
Sleep apnea syndrome/apnea	53 (48)	7.3 (1.5–19.1)	27 F, 26 M	2.0 (0.1–10.0)	20	30	3
Tonsillar hypertrophy	15 (15)	4.3 (1.2–12.4)	11 F, 4 M	1.6 (0.2–6.0)	9	6	
Obstructive airways disorder	3 (3)	4.6 (3.9–7.5)	1 F, 2 M	1.4 (0.8–2.8)	1	2	
Snoring	20	6.0 (1.0–10.1)	12 F, 8 M	1.3 (0.0–6.6)	5	14	1
Adenoidectomy/adenotonsillectomy	17	5.5 (2.7–11.4)	10 F, 7 M	2.3 (0.2–4.2)		16	1
Hip surgery	3 (3)	4.3 (3.1–11.1)	2 F, 1 M	1.3 (0.7–2.0)		3	
Hepatectomy	1 (1)	9.8	1 M	0.5		1	
Circulatory collapse	1 (1)	10.8	1 F	0.9		1	

Abbreviations: BIH, benign intracranial hypertension; F, female; M, male; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a] GH related according to the local site investigators' opinion (without central adjudication).

[b] Cryptorchidism, scoliosis, and psychiatric disorders are recognized conditions of patients with PWS.

four months after initiation of GH treatment with somnolence and cough and case 6 two weeks after GH initiation with respiratory insufficiency after salbutamol discontinuation.

Discussion

This study describes, to our knowledge, the largest international cohort of 522 prepubertal children with PWS treated for three consecutive years and 173 adolescents who reached adult height after a mean duration of eight years of GH treatment. KIGS was a cumulative database, and the number of patients registered continued to increase over the years. The volume of the KIGS data provides a unique opportunity to evaluate safety and the growth and weight response to GH treatment before and during puberty in children with PWS.

In line with previous studies, height SDS and Ht-MPH SDS normalized during three years of GH treatment (9, 11, 13, 25). In the adolescent group, height SDS and Ht-MPH SDS had normalized by entering puberty but significantly decreased during puberty. Nevertheless,

Table 6. Deaths in Patients With PWS Treated With GH

Case No.	PWS Genetic Diagnosis	Death Year	Age at Death, y	Age at GH Start, y	BMI SDS[a]	Height SDS[a]	Weight SDS[a]	GH Dose, mg/kg/wk	Cause of Death
1	Methylation imprinting defect	2009	1.3	1.3	2.0	−4.3	−1.3	0.07	Disseminated intravascular coagulation
2	Deletion 15q11-q13	2002	2.1	0.6	0.9	−1.1	0.2	0.33	Cardiac and respiratory arrest
3	Deletion 15q11-q13	2007	2.3	1.0	−1.2	1.0	0.4	0.16	Immunodeficiency
4	Deletion 15q11-q13	2009	3.6	3.3	4.0	−2.1	2.1	0.29	Pneumonia[b]
5	Unknown	2001	4.7	4.6	5.8	0.6	5.7	0.24	Sleep apnea
6	Abnormal methylation pattern	2001	8.0	8.0	4.0	−1.3	3.1	0.15	Respiratory insufficiency[b]
7	Deletion 15q11-q13	2009	11.8	1.5	2.2	−1.1	1.3	0.14	Accidental death (fall)
8	Deletion 15q11-q13	2004	12.0	10.1	0.0	−2.0	−1.0	0.23	Death in the bath
9	Deletion 15q11-q13	2005	15.2	7.0	−0.4	−3.2	−2.1	0.21	Stomach perforation
10	Unknown	1995	15.8	15.2	3.5	−4.0	1.7	0.10	Pneumonia
Events occurred after stopping GH treatment									
11	Deletion 15q11-q13	2001	18.4	16.7	4.0	−3.4	3.4	0.04	Unknown[c]
12	Methylation study absent 221 bp	2006	24.2	12.2	3.6	−3.3	2.4	0.14	Unknown[c]

[a]Data obtained prior to the event.

[b]Patients 4 and 6 had autopsies.

[c]This event occurred after stopping GH treatment.

adult height SDS was −1.2, resulting in an acceptable mean height of 170 cm in boys and 156 cm in girls. A reduced pubertal growth spurt is also observed in non-GH-treated PWS adolescents (31) and is probably explained by the fact that children with PWS have a normal onset of puberty but a delay in pubertal development after Tanner stage 3 (35, 36).

In the adolescent group, data on pubertal development and sex hormone treatment were not available. Data regarding the effect of long-term GH treatment in combination with optimal sex hormone replacement treatment during adolescence on adult height are lacking, but with adequate sex hormone substitution, some additional height gain could be expected. A previous study from Sweden reported a normal adult height SDS in 22 young adults with PWS after 10 years of GH treatment without sex hormone substitution (13). This could be related to the fact that Scandinavian people are in general one of the tallest populations. In addition, midparental height SDS is positively associated with adult height SDS in PWS. Thus, by using international references values, it could be expected that Swedish children with PWS are taller. Another reason for a lower growth spurt could be related to the high incidence of scoliosis in children with PWS (37) and also reported in the KIGS as a frequent AE or SAE. Although scoliosis is reported at all ages in PWS, the incidence increases with age to 80% above the age of 10 years (37).

BMI SDS increased during three years of GH treatment in the prepubertal children, but BMI remained on average below the +2 SDS, even during the long-term GH treatment, in contrast to the natural course of increasing obesity in children with PWS. Nowadays, the standard GH dose for children with PWS is 1 mg/m^2/d (0.23 mg/kg/wk) (38), and as shown in a GH dose-response study, children with PWS needed a GH dose of at least 1 mg/m^2/d to optimize and maintain their body composition (24). With a lower dose, the lean body mass declined and fat mass percentage increased, whereas a higher dose improved body composition even more. The mean GH dose in this KIGS cohort was 0.22 mg/kg/wk. Because KIGS is a noninterventional observational study and the GH treatment management was at the discretion of the physician, it could be that the GH dose in a subgroup may have been too low to improve body composition and BMI. Moreover, it is known that body composition does not normalize compared with reference children (25). Nowadays, the health of children with PWS has improved by the combination of early diagnosis, better awareness of the parents, a strict diet and exercise program, and GH treatment.

The KIGS database did not include information on dual-energy X-ray absorptiometry data. Nevertheless, we conclude that after three years of GH treatment, a height SDS of −0.3 and a BMI SDS of 1.5 indicate a successful treatment of children with PWS, knowing that the untreated, natural course of PWS leads to morbid obesity in many patients. In the adolescent group, BMI SDS remained stable during long-term GH treatment. Their BMI SDS was at the start already higher than in the

prepubertal group, and they were older at initiation of GH treatment. Still, GH treatment was able to stabilize BMI until adult height, but earlier initiation of GH treatment might have stabilized BMI at a lower SDS. Moreover, early initiation of GH treatment has also shown its benefits in motor and mental development in young children with PWS (14, 39).

There was a shift from delayed bone maturation in the younger children toward advanced bone maturation in the older children. The advanced bone maturation in the children with a mean age above seven years might be related to adrenarche, typically occurring early in many children with PWS (40–42).

For safety analyses, KIGS could provide data of 2332 patients with 8783 treatment years. The rate of minor AEs was comparable with previous studies (43, 44) and also included AE reports about syndrome-specific features of PWS, such as scoliosis, cryptorchidism, sleep apnea, and psychiatric disorders. It is very difficult to determine whether an AE or SAE is related to PWS or to GH treatment, especially because the data were provided by physicians from different regions. It is well known, for example, that sleep apnea syndrome and scoliosis are features of PWS (4), and previous clinical studies showed that GH treatment does not aggravate onset and progression of scoliosis and sleep apnea (45, 46).

Diabetes and insulin resistance were reported in KIGS in a few cases. Adults with PWS are at increased risk of type 2 DM, but a recent study in GH-treated adults found diabetes only in patients who did not follow the recommended lifestyle (47). It is known that one of the physiological effects of GH is to reduce insulin sensitivity. Therefore, treatment with GH in PWS could increase the risk of diabetes, although long-term beneficial effects of GH on body composition seem to compensate this risk (9, 25, 38). At the individual level, some patients might have a familial predisposition to diabetes, and thus it is recommended to monitor glucose metabolism in PWS carefully, especially during GH treatment and in obese patients.

High IGF-1 levels were reported in only 28 children. According to several studies, high IGF-1 levels during GH treatment are very common in children with PWS (25, 48, 49). Thus, it seems that high IGF-1 levels were underreported in the KIGS database, probably because physicians just lowered the GH dose. This might also explain why we observed a lower GH dose during puberty than before puberty. A recent study observed that there was a much poorer correlation between serum insulin-like growth factor bioactivity and serum IGF-1 in GH-treated children with PWS than was observed among controls, largely because of greater sequestration of IGF-1 in ternary complexes in children with PWS. Thus, total IGF-1 concentrations may be an inappropriate indicator for GH dosing in children with PWS (48).

Two of the 2332 patients were diagnosed with leukemia. One child had juvenile chronic myelomonocytic leukemia at the age of 0.9 years just after the initiation of GH treatment, and one child aged 8.7 years had T-cell type acute leukemia after 3.5 years of GH treatment. A retrospective study, investigating the incidence of cancer in 1160 non-GH-treated PWS patients, observed eight patients with cancer, of whom three had myeloid leukemia vs 0.075 expected leukemia in the age-matched reference population (50). They concluded that persons with PWS have an increased risk of myeloid leukemia but not other cancers (50).

When reporting an AE or an SAE to KIGS, physicians were asked if they thought the AE or SAE was related to GH treatment. We observed a great variation in the answers. This may be explained by the fact that in the past 25 years, considerable research has focused on the effects and safety of GH treatment. This could have influenced the opinion of physicians on whether an AE or SAE was related to GH treatment or the underlying conditions.

From the KIGS database, 12 deaths were reported, of which 10 were in children receiving GH at the time of death. This appears to be lower than the reported 3% annual mortality rate in patients with PWS younger than 30 years (26). This seems reassuring, but we must acknowledge that KIGS as an observational study was not designed to provide reliable mortality rates. On the other hand, although some events may have been underreported in the KIGS database, underreporting of death seems unlikely at least for the duration that the patient was enrolled in the study.

One 15-year-old female, with a normal BMI, died of gastric perforation. Gastric problems have been described in patients with PWS, and gastric perforation is a major risk for people with PWS (51). Although GH treatment improves body composition and BMI (25), children with PWS continue to have hyperphagia and can consume large amounts of food at one time. Hyperphagia with food-seeking behavior can, when uncontrolled, lead to life-threatening gastric dilatation with perforation (52).

One child died suddenly in the bathtub, one child died of shock followed by disseminated intravascular coagulation, four died of pneumonia, and one died after diarrhea and vomiting followed by a cardiorespiratory arrest. Central adrenal insufficiency in patients with PWS might contribute to the high rate of unexplained and sudden deaths in these patients, particularly during infection-related stress (21, 53). Sleep apnea syndrome was reported in 53 children. The combination of sleep-related breathing disorder and central adrenal insufficiency may deteriorate the condition of children with

PWS with an infection (22). Physicians, therefore, should consider treatment with hydrocortisone stress medication during acute illness and surgery in children with PWS (21).

In conclusion, these unique data from a very large group of GH-treated children with PWS demonstrate that GH treatment, with a mean dose of 0.22 mg/kg/wk, significantly improved linear growth and adult height. During GH treatment, BMI SDS remained on average below the +2 SDS. The number of reported deaths in GH-treated children with PWS in KIGS seems low compared with the high annual mortality rate of 3% in untreated patients with PWS. However, safety issues, such as diabetes, sleep-related breathing disorders, gastric problems, and infections, should be closely monitored in children with PWS, with and without GH treatment.

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