Sleep-Related Breathing Disorders in Young Adults With Prader-Willi Syndrome: A Placebo-Controlled, Crossover GH Trial

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Context: Sleep-related breathing disorders (SRBD) are common in people with Prader-Willi syndrome (PWS). Young adults with PWS benefit from GH continuation after attaining adult height by maintaining the improved body composition obtained during childhood. There are, no studies about the effects of GH on SRBD in young adults with PWS who were treated with GH during childhood.

Objective: Investigate the effects of GH vs placebo on SRBD in young adults with PWS who were treated with GH during childhood and had attained adult height.

Design: Two-year, randomized, double-blind, placebo-controlled, crossover study in 27 young adults with PWS, stratified for sex and body mass index.

Setting: Dutch PWS Reference Center.

Intervention: Crossover intervention with GH (0.67 mg/m^2/d) and placebo, both over one year.

Main Outcome Measures: Apnea hypopnea index (AHI), obstructive apnea index (OAI), central apnea index (CAI), measured by polysomnography.

Results: Compared with placebo, GH did not increase AHI, CAI, or OAI ($P > 0.35$). The effect of GH vs placebo was neither different between men and women, nor between patients with a deletion or maternal uniparental disomy/imprinting center defect. After two years, there was no difference in AHI, CAI, or OAI compared with baseline ($P > 0.18$). Two patients (7%) fulfilled the criteria of obstructive sleep apnea regardless of GH or placebo.

Conclusions: GH compared with placebo does not cause a substantial increase in AHI, CAI, or OAI in adults with PWS who were treated with GH during childhood and have attained adult height. Our findings are reassuring and prove that GH can be administered safely. (***J Clin Endocrinol Metab*** **104: 3931–3938, 2019)**

Prader-Willi syndrome (PWS) is a genetic disorder that results from the lack of expression of the PWS region on the paternally inherited chromosome 15, caused by a deletion, maternal uniparental disomy (mUPD), imprinting center defect (ICD), or translocation (1, 2). Hypothalamic dysfunction is an underlying cause for many symptoms

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Abbreviations: AHI, apnea hypopnea index; BMI, body mass index; CAI, central apnea index; FM, fat mass; ICD, imprinting center defect; LBM, lean body mass; mUPD, maternal uniparental disomy; OAI, obstructive apnea index; OSA, obstructive sleep apnea; PSG, polysomnography; PWS, Prader-Willi syndrome; Sao_2, oxygen saturation; SDS, SD score; SRBD, sleep-related breathing disorders.

related to PWS, which include muscular hypotonia and failure to thrive during infancy, and short stature, hyperphagia, and obesity during childhood and adulthood. Both children and adults with PWS have an abnormal body composition with an increased fat mass (FM) and low lean body mass (LBM), even if there is no obesity (1, 3).

Sleep-related breathing disorders (SRBD) are common in patients with PWS, causing poor sleep quality and excessive daytime sleepiness (4–6). PWS children have a high apnea hypopnea index (AHI), which is mainly caused by central apneas and hypopneas (7). Obstructive apneas occur more frequently in children and adults with a higher body mass index (BMI) (7, 8). There are several other factors that are thought to influence SRBD in PWS, such as facial dysmorphia, lack of response to hypoxia and hypercapnia, and airway collapse caused by pharyngeal wall hypotonia and adenoid/tonsil hypertrophy (4, 9). We have also demonstrated that there might be an alteration in central ventilatory regulation during stress (10).

Currently, children with PWS are treated with long-term GH improving the abnormal body composition and mental and motor development, cognition, adaptive functioning, and linear growth (11–16). There have been some reports on SRBD in PWS discussing the safety of GH treatment in children with PWS. We have described an insignificant decline in AHI after six months of GH treatment in 35 prepubertal children with PWS and a recent review has concluded that GH can be administered safely, provided that SRBD is monitored and treated appropriately (7, 17).

When young adults with PWS have attained adult height, they must stop GH treatment, unless they are GH deficient. Recently, we found that young adults with PWS benefit from continuation of GH compared with placebo by maintaining the improved body composition obtained during childhood (18). To our knowledge, there are no studies of the effects of GH vs placebo on SRBD in young adults with PWS who were treated with GH during childhood.

Therefore, we investigated the effects of one year of GH vs one year of placebo on SRBD, measured by polysomnography (PSG), in young adults with PWS who had attained adult height and were treated with GH during childhood in a two-year, randomized, double-blind, placebo-controlled crossover study. We hypothesized that GH would not negatively influence SRBD. Second, we investigated the prevalence of obstructive sleep apnea (OSA) in our cohort of young adults with PWS.

Patients and Methods

Subjects

Inclusion criteria were (i) genetically confirmed diagnosis of PWS; (ii) GH treatment during childhood for at least two years until attaining adult height and on GH at time of inclusion; and (iii) adult height attainment, defined as complete epiphyseal fusion and a height velocity less than 0.5 cm per six months. Exclusion criteria were medication to reduce weight or fat or noncooperative behavior.

From June 2008 to January 2014, 33 young adults with PWS fulfilled the inclusion criteria. Three refused participation owing to too large a burden of hospital visits, and two did not want to continue the daily injections. Of the 28 included patients, one 16.7-year-old participant (BMI 25.0 kg/m^2) died of gastric rupture and necrosis three months after inclusion while receiving placebo. Her data were excluded from the present analyses.

During childhood, patients were treated with the standard GH dose of 1.0 mg/m^2/d. High serum IGF-1 levels caused lowering of the GH dose in eight children. Eleven patients received an adult dose of sex steroid replacement therapy (40.7%), eight patients were using thyroid hormone supplementation (29.6%), two were taking modafinil (7.4%), and one patient was using risperidone and citalopram.

Design

A two-year, randomized, double-blind, placebo-controlled, crossover study was conducted to investigate the effects of one year of GH treatment vs one year of placebo on sleep-related breathing disorders (SRBD). Young adults were stratified according to sex and BMI (below/above 25 kg/m^2) and then randomly and blindly assigned to receive one year of subcutaneous injections once daily at bedtime of either 0.67 mg/m^2/d GH (Genotropin®, 5 mg/mL; Pfizer) or one year of identical appearing placebo (Pfizer), after which they crossed over to the alternative treatment of another year. An independent statistician generated the random allocation sequence. Investigators, patients, and parents were blinded for the allocation. An independent physician monitored the safety during the study. Unblinding was not necessary.

Measurements

Patients were examined every 3 months by the PWS team of the Dutch Growth Research Foundation, in collaboration with pediatric endocrinologists and pediatricians in the Netherlands. At each visit, the injection dose was adjusted to the calculated body surface area. In addition, patients visited the Erasmus Medical Center at baseline, 6, 12, 18, and 24 months, to allow staff to obtain height, weight and body composition.

FM and LBM were measured by DXA (Lunar Prodigy; GE Healthcare, Chalfont St. Giles, UK). All scans were made on the same machine, with daily quality assurance. FM was expressed as percentage of total body weight (FM%). FM% SD score (SDS) and LBM SDS were calculated according to age- and sex-matched Dutch reference values (19). Standing height was measured with a calibrated Harpenden stadiometer (Holtain Ltd., Crosswell, UK), weight was determined on a calibrated scale (ServoBalance KA-20-150S, Servo Berkel Prior, Katwijk, Netherlands), and BMI was calculated. Height, weight and BMI were expressed as SDS (20, 21). SDS values were calculated with GrowthAnalyser 4.0 (available at www.growthanalyser.org).

At the start of the study, after one year, and after two years, polysomnography (PSG) was performed at the Sleep-Wake Center SEIN, Zwolle, Netherlands. Young adults were admitted to the sleep center at 5:00 PM, accompanied by one parent. We asked about typical symptoms of OSA at each visit.

Table 1. Baseline Characteristics of the Total Group and Per Treatment Schedule

	PWS (n = 27)	Placebo/GH (n = 14)	GH/Placebo (n = 13)
Boys/girls, n	8/19	4/10	4/9
Genetic subtype, deletion/mUPD/ICD/translocation	9/15/2/1	2/10/1/1[a]	7/5/1/0
Age, y	17.2 (1.8)	17.2 (2.2)	17.3 (1.2)
Duration of childhood GH treatment, y	8.7 (3.2)	8.9 (3.8)	8.4 (2.5)
Adult height, SDS	−1.3 (0.9)	−1.3 (0.9)	−1.2 (0.9)
BMI, kg/m^2	24.1 (4.0)	24.6 (4.1)	23.6 (4.1)
BMI, SDS	0.9 (1.3)	1.0 (1.2)	0.7 (1.3)
IGF-1, SDS	2.2 (1.0)	1.8 (1.2)	2.5 (0.8)
FM%	38.0 (10.9)	39.4 (10.9)	36.4 (11.0)
FM%, SDS	1.7 (0.7)	1.8 (0.7)	1.6 (0.7)
Lean mass, kg	37.5 (7.8)	37.1 (8.3)	37.9 (7.6)
Lean mass, SDS	−1.6 (1.0)	−1.6 (1.0)	−1.6 (0.9)

Data expressed as mean (SD).

[a]The group that received GH in the second phase of the study consisted of more patients with an mUPD or ICD ($P = 0.046$).

Recordings included electroencephalogram, electro-oculogram, one-channel derivation of ECG, and surface electromyography of the submental muscle and both anterior tibial muscles. Nasal–oral airflow was monitored by nasal pressure prongs fixed in the nose, respiratory effort by thoraco-abdominal gauges, and oxygen saturation (Sa_{O_2}) by pulse oximetry. All polysomnographic records were evaluated independently by two persons, both certified in PSG analysis, and scored according to the adult rules of the American Academy of Sleep Medicine Manual (22). Seventeen patients also had a PSG during childhood GH treatment.

An obstructive apnea was defined as a reduction of airflow of 90% or more during at least 10 seconds with continuous breathing effort during the apnea. An apnea was considered central if the respiratory event was associated with absent breathing effort for 10 seconds or more with an arousal or a decrease in Sa_{O_2} of at least 3%. Hypopneas were defined as a reduction of airflow of at least 30% during 10 seconds or more, with an arousal or a decrease in Sa_{O_2} of at least 3% (22). The number of obstructive, central and mixed apneas and hypopneas were counted during the total sleep time and an apnea hypopnea index (AHI) was calculated per hour of sleep. The obstructive apnea index (OAI) was defined as the number of obstructive apneas per hour of sleep and the central apnea index (CAI) as the number of central apneas per hour of sleep. OSA was defined as an AHI ≥ 5 events per hour associated with typical symptoms of OSA (*e.g.*, unrefreshing sleep, daytime sleepiness, fatigue or insomnia, awakening with gasping or choking sensation, snoring, witnessed apneas) or an AHI ≥15 events per hour, regardless of symptoms (23).

Assays

Blood samples were collected after an overnight fast and serum IGF-1 levels measured in one laboratory. IGF-1 was measured using an immunometric technique on Immulite 1000 (LKGF1; Siemens Medical Solutions Diagnostics) with an interassay variation <7.3%. IGF-1 levels were expressed as SDS, adjusting for age and sex (24).

Statistics

Statistical analyses were performed with SPSS 24.0. Data were expressed as mean (SD) in case of a Gaussian distribution and as median [interquartile range (IQR)]in case of a non-Gaussian distribution. Sex and genotypic differences in AHI, CAI, and OAI were calculated by independent samples *t* tests or Mann-Whitney U tests, depending on the distribution.

Effects of GH vs placebo were calculated using the following formulas for (i) AHI: (ΔAHI during GH − ΔAHI during Placebo)/2; (ii) (ΔCAI during GH − ΔCAI during Placebo)/2; and (iii) (ΔOAI during GH − ΔOAI during Placebo)/2. The mean outcome of these calculations was compared with 0 using a one-sample *t* test. We did not find carryover or period effects, which were analyzed by comparing the change in AHI, CAI, and OAI during GH and placebo between the two treatment sequences (GH followed by placebo and placebo

Table 2. Baseline Sleep-Related Breathing in the Total Group and Per Treatment Schedule

	PWS (n = 27)	Placebo/GH (n = 14)	GH/Placebo (n = 13)
Total sleep time, h	8.1 (7.0; 8.7)	8.4 (7.7; 8.9)[a]	7.4 (6.5; 8.1)
AHI	3.6 (1.4; 4.7)	3.4 (1.0; 4.7)	3.8 (1.7; 4.8)
CAI	1.1 (0.6; 2.0)	1.0 (0.5; 2.3)	1.1 (0.6; 1.9)
OAI	0.0 (0.0; 0.3)	0.0 (0.0; 0.2)	0.0 (0.0; 0.6)
Duration longest apnea, sec	22.2 (18.6; 27.9)	23.3 (20.1; 28.1)	20.4 (18.1; 25.1)
Median sleep Sa_{O_2},%	96.0 (95.5; 96.7)	96.1 (94.6; 96.7)	96.0 (95.6; 96.8)
Minimum Sa_{O_2}, %	90.0 (86.0; 92.0)	89.0 (83.0; 92.0)	91.0 (88.5; 92.5)

Data expressed as median (IQR).

[a]Total sleep time was significantly longer in the patients who received GH in the second phase of the RCT ($P = 0.02$).

followed by GH) and during the first and second year of the study, respectively. AHI, CAI, and OAI at start and after two years in the current study were compared with AHI, CAI, and OAI during the childhood PSG using Wilcoxon signed ranks tests. Correlations between AHI, CAI, or OAI and height SDS, BMI SDS, FM% SDS, or IGF-1 SDS were calculated by Spearman correlation analysis. P values < 0.05 were considered statistically significant.

Study approval

Written informed consent was obtained from patients and parent(s)/caregiver(s). The study protocol was approved by the Medical Ethics Committee of Erasmus University Medical Center, Rotterdam, and registered at the Dutch Trial Register (www.trialregister.nl, NTR1038).

Results

Baseline characteristics at adult height

Clinical characteristics

Baseline clinical characteristics of the 27 young adults with PWS who participated in this study after attainment of adult height are shown in Table 1. Mean (SD) age and BMI were 17.2 (1.8) years and 0.9 (1.3) SDS, respectively. The group that received GH in the second year of the study consisted of more patients with an mUPD or ICD ($P = 0.046$). There were no other differences between the treatment groups (all $P > 0.24$).

Sleep-related breathing

Baseline median (IQR) total sleep time was 8.1 (7.0; 8.7) hours and AHI 3.6 (1.4; 4.7) events per hour (Table 2). Total sleep time was longer in the patients who received GH in the second phase of the randomized controlled trial ($P = 0.02$). The other polysomnographic characteristics were similar in both treatment arms (all $P > 0.06$). Four participants had an abnormal AHI of ≥5 events per hour at baseline (14.8%), but none of them had typical symptoms of OSA and therefore did not fulfill the current criteria of OSA in adults (23).

Male PWS patients had a higher median AHI and CAI than female PWS patients (4.7 vs 2.1 and 1.9 vs 0.8, respectively, both $P = 0.01$). Median OAI was 0 in both male and female patients ($P = 0.67$). There was no difference in AHI and CAI between young adults with a deletion and an mUPD or ICD (all $P > 0.24$). OAI was slightly higher in patients with an mUPD or ICD than in patients with a deletion (0.2 vs 0.0, $P = 0.04$). Neither height SDS nor BMI SDS, FM% SDS, or IGF-1 SDS at adult height were associated with AHI, CAI, or OAI at adult height.

Sleep-related breathing during GH vs placebo

Compared with placebo, one year of GH did not increase AHI, CAI, or OAI ($P > 0.35$) (Fig. 1). The effect of GH vs placebo on AHI, CAI, or OAI was neither different between boys and girls ($P > 0.23$), nor between young adults with a deletion or an mUPD or ICD ($P > 0.14$). After two years, there was no difference in AHI, CAI, or OAI compared with baseline, regardless of GH or placebo ($P > 0.18$).

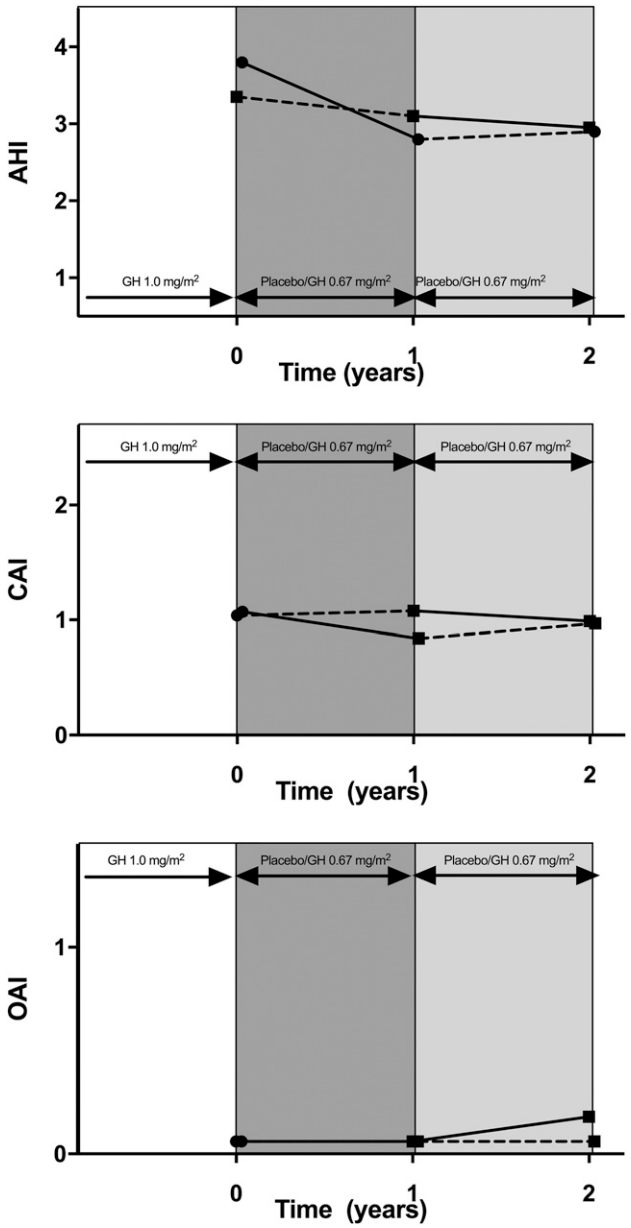

Figure 1. AHI, CAI, and OAI during 1 y of GH and 1 y of placebo, presented as median. The dotted lines represent the period with placebo. There were no substantial changes during GH vs placebo.

Table 3 shows the 11 patients with an AHI of ≥5 events per hour during at least one of the PSGs performed during the two-year study. At start of the study, 4 patients had an AHI of ≥5 events per hour. Seven patients developed an AHI of ≥5 events per hour during the study, 5 during placebo, and 2 during GH. Two fulfilled the current criteria of OSA (7% of the total group),

Table 3. Patient With an AHI of Five or More Events Per Hour During the Study

Patient No. (Genotype)	Age at Baseline	Sex	Complaints	Tonsillar Hypertrophy		GH Phase	AHI At Baseline	AHI After 1 y	AHI After 2 y
1 (DEL)	18.9	M	No	No	AHI	1	5.2	5.5	7.4
					BMI (kg/m^2)		18.4	18.4	19.6
2 (DEL)	18.3	F	No	No	AHI	1	6.6	11.3	7.0
					BMI (kg/m^2)		29.9	31.4	36.3
3 (DEL)	17.4	F	Mild	Mild	AHI	1	1.7	4.3	5.4
					BMI (kg/m^2)		28.6	32.2	31.6
4 (UPD)	17.9	M	No	No	AHI	1	4.5	5.0	9.9
					BMI (kg/m^2)		19.2	18.8	20.3
5 (UPD)	15.9	F	No	No	AHI	2	5.0	3.1	4.6
					BMI (kg/m^2)		24.1	24.9	25.9
6 (DEL)	20.2	M	No	No	AHI	2	11.1	3.1	3.0
					BMI (kg/m^2)		24.3	24.2	24.6
7 (UPD)	14.5	F	Mild	Mild	AHI	2	1.9	1.6	5.8
					BMI (kg/m^2)		30.8	36.4	36.5
8 (ICD)	18.8	M	Moderate	No	AHI	2	4.7	4.7	5.8
					BMI (kg/m^2)		24.9	26.4	24.4
9 (UPD)	18.4	M	No	No	AHI	2	4.7	5.9	—
					BMI (kg/m^2)		32.3	322	32.3
10 (UPD)	16.1	F	No	No	AHI	2	4.2	6.6	3.7
					BMI (kg/m^2)		24.6	262	26.0
11 (UPD)	18.7	M	No	No	AHI	2	0.6	8.1	2.9
					BMI (kg/m^2)		18.5	19.6	19.5

Patients 1 through 4 received one year of GH after one year, while patients 5 through 11 received one year of GH after two years. Patient 3 and 7 fulfilled the diagnostic criteria of OSA, because they also developed mild complaints of snoring and daytime sleepiness. Patient 8 was also diagnosed with narcolepsy and therefore did not fulfill the diagnostic criteria of OSA.

Abbreviations: DEL, deletion; ICD, imprinting center defect; UPD, uniparental disomy.

because they also developed mild complaints of snoring and daytime sleepiness, 1 during GH, the other during placebo (23). AHI in these 2 patients consisted mainly of hypopneas, OAI being 0 and 1.2 events per hour. Both were obese and had tonsillar hypertrophy, for which they were referred to an otolaryngologist. One patient with an AHI $\geq$5 events per hour and moderate complaints of daytime sleepiness did not fulfill the criteria of OSA, because he was also diagnosed with narcolepsy and taking modafinil during the study.

Sleep-related breathing during childhood and adulthood

Seventeen participants (62.9%) had a PSG during childhood GH treatment (Table 4). AHI ranged from 1.0 to 14.7 events per hour and 6 children had an AHI of $\geq$5 events per hour (35%). Only two of these children were reported to have obstructive apneas, OAI being 1.9 and 2.0 events per hour.

Compared with the childhood PSG, AHI, CAI, and OAI were not higher at adult height or after two years in the study (all $P > 0.21$). The change in AHI, CAI, or OAI from childhood to adulthood was neither different between boys and girls ($P > 0.09$), nor between patients with a deletion or an mUPD or ICD ($P > 0.13$).

Discussion

This randomized, double-blind, placebo-controlled crossover GH study in young adults with PWS who were treated with GH during childhood until attainment of adult height, investigated the effects of GH vs placebo on sleep-related breathing. We have previously shown that young adults with PWS benefit from continuation of GH by maintaining the improved body composition obtained during childhood, without safety concerns regarding their metabolic health profile (18, 25). Our study demonstrates that, compared with placebo, GH does not cause an increase in AHI, CAI, or OAI in young adults with PWS. These findings are reassuring and prove that GH can be administered safely with regard to SRBD.

Only one other study examined SRBD during GH treatment in 10 adults with PWS (26). The authors performed a PSG at baseline and 6 weeks after the initiation of GH treatment. Nine of 10 adults showed an improvement in AHI. One adult with worsening of the AHI had a concurrent respiratory infection and tonsillar hypertrophy (26). In children with PWS, several studies investigated the effects of GH on SRBD (7, 27–29). We previously found an insignificant decline in AHI after six months of GH treatment in 35 prepubertal children with

Table 4. Sleep-Related Breathing During Childhood, at Adult Height, and After 2 Y

	Childhood (n = 17)	Adult Height (n = 17)	After 2 y (n = 14)
Age, y	10.0 (8.0; 11.5)	17.4 (15.2; 18.3)[a]	19.3 (16.7; 20.4)[a]
Total sleep time, h	8.4 (7.7; 8.7)	8.2 (7.2; 8.9)	7.9 (7.4; 9.0)
AHI	4.1 (2.6; 6.2)	3.8 (1.4; 4.8)	3.0 (1.2; 5.5)
CAI	1.2 (0.6; 2.8)	1.0 (0.5; 2.1)	1.0 (0.3; 1.5)
OAI	0.0 (0.0; 0.4)	0.0 (0.0; 0.9)	0.0 (0.0; 0.5)
Duration longest apnea, sec	18.0 (16.0; 24.5)	22.3 (19.3; 27.2)	21.9 (17.8; 33.8)
Median sleep Sao_2,%	92.0 (87.0; 98.0)	96.0 (95.5; 96.5)[a]	96.1 (95.0; 97.0)[a]
Number of awakenings	13 (7; 18)	14 (11; 21)	16 (11; 26)[a]

Data expressed as median (IQR).

[a] $P = 0.05$ compared with childhood PSG.

PWS with a median age of 6.0 years at start of GH (7). Al-Saleh *et al.* (27) reported no change in obstructive apnea hypopnea index (OAHI) and CAI during 2 years of GH treatment in 15 children with PWS with a median age of 3.7 years at start of GH. The same research group investigated OAHI and CAI in 28 young children with PWS and found an improvement of the CAI and no difference in OAHI between the baseline and follow-up PSG, regardless of GH treatment (28).

Overall, studies regarding the effects of GH on SRBD in children and adults with PWS conclude that GH treatment does not negatively influence AHI. However, medical professionals should be aware that (mild) upper respiratory tract infections and/or adenotonsillar hypertrophy can cause increased obstructive apneas (7, 29).

The reported prevalence of OSA in people with PWS is variable, because of wide age ranges, different diagnostic criteria, and a potential referral bias (5, 6, 30). Recent guidelines define OSA in adults as an AHI of ≥5 events per hour combined with typical complaints for OSA (*e.g.*, daytime sleepiness, snoring, or witnessed apneas), or an AHI of ≥15 events per hour regardless of complaints (23). According to these guidelines, two participants in our study (7%) fulfilled the diagnostic criteria of OSA, regardless of GH or placebo. However, only one of them had obstructive apneas during sleep with an OAI of only 1.2 events per hour. Based on these patients we would suggest, in addition to evaluating AHI, to specifically assess the number of obstructive apneas. OAI might be a more accurate parameter than AHI for diagnosing OSA.

We could compare a PSG performed during childhood GH treatment with a PSG performed at adult height and after two years in the current study in 17 and 14 participants, respectively. There was no difference in AHI, OAI, or CAI between the childhood PSG and the PSG at adult height or the PSG after two years in the study, regardless of GH treatment or placebo. During the childhood PSG, 35% of children had an AHI of ≥5 events per hour. At start and finish of the current study, respectively, 15% and 22% of young adults, had an AHI of ≥5 events per hour. These data demonstrate that long-term GH treatment during childhood has no negative consequences with regard to the prevalence of SRBD in young adults with PWS.

We have previously shown that long-term GH treatment in combination with a healthy lifestyle can counteract the clinical course of PWS during childhood and reduce the prevalence of morbid obesity (12). Median baseline BMI of the participants in the current study was 24.1, which is much lower than (young) adults with PWS who were never treated with GH. Also, unlike previous reports, we did not find a correlation between AHI and BMI or FM% SDS. It is likely that as a result of the reduced prevalence of obesity in our cohort of young adults with PWS, SRBD occurs less commonly.

The current consensus guideline for GH treatment in PWS recommends performing a PSG before and three to six months after starting GH treatment in children with PWS (11). Based on our data in adults with PWS, we would not recommend a standard PSG at attainment of adult height in nonobese patients with PWS who were treated with GH during childhood and will continue GH treatment in adulthood. However, clinical signs of SRBD need to be monitored and, when indicated, a PSG should be performed.

In conclusion, our study shows that, compared with placebo, AHI does not increase during GH treatment in young adults with PWS who were previously treated with GH during childhood. GH treatment has positive effects on body composition and health profile in adults with PWS. The results of the current study are reassuring and prove that GH can be administered safely. However, clinical signs of SRBD need to be monitored in children and adults with PWS, because obstructive apneas occur in patients with adenotonsillar hypertrophy and/or (mild) upper respiratory tract infections.

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References and Notes

1. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. *Genet Med*. 2012;**14**(1):10–26
2. Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. *J Endocrinol Invest*. 2015;**38**(12):1249–1263.
3. Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M; speakers contributors at the Second Expert Meeting of the Comprehensive Care of Patients with PWS. Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2008;**93**(11):4183–4197.
4. Pavone M, Caldarelli V, Khirani S, Colella M, Ramirez A, Aubertin G, Crinò A, Brioude F, Gastaud F, Beydon N, Boulé M, Giovannini-Chami L, Cutrera R, Fauroux B. Sleep disordered breathing in patients with Prader-Willi syndrome: a multicenter study. *Pediatr Pulmonol*. 2015;**50**(12):1354–1359.
5. Sedky K, Bennett DS, Pumariega A. Prader Willi syndrome and obstructive sleep apnea: co-occurrence in the pediatric population. *J Clin Sleep Med* 2014;**10**(4):403–409.
6. Ghergan A, Coupaye M, Leu-Semenescu S, Attali V, Oppert JM, Arnulf I, Poitou C, Redolfi S. Prevalence and phenotype of sleep disorders in 60 adults with Prader-Willi syndrome. *Sleep*. 2017;**40**(12):40.
7. Festen DA, de Weerd AW, van den Bossche RA, Joosten K, Hoeve H, Hokken-Koelega AC. Sleep-related breathing disorders in prepubertal children with Prader-Willi syndrome and effects of growth hormone treatment. *J Clin Endocrinol Metab*. 2006;**91**(12):4911–4915.
8. Clift S, Dahlitz M, Parkes JD. Sleep apnoea in the Prader-Willi syndrome. *J Sleep Res*. 1994;**3**(2):121–126.
9. Lindgren AC, Hellström LG, Ritzén EM, Milerad J. Growth hormone treatment increases CO(2) response, ventilation and central inspiratory drive in children with Prader-Willi syndrome. *Eur J Pediatr*. 1999;**158**(11):936–940.
10. de Lind van Wijngaarden RF, Joosten KF, van den Berg S, Otten BJ, de Jong FH, Sweep CG, de Weerd AW, Hokken-Koelega AC. The relationship between central adrenal insufficiency and sleep-related breathing disorders in children with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2009;**94**(7):2387–2393.
11. Deal CL, Tony M, Höybye C, Allen DB, Tauber M, Christiansen JS; 2011 Growth Hormone in Prader-Willi Syndrome Clinical Care Guidelines Workshop Participants. GrowthHormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2013;**98**(6):E1072–E1087.
12. Bakker NE, Kuppens RJ, Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Bindels-de Heus GC, Bocca G, Haring DA, Hoorweg-Nijman JJ, Houdijk EC, Jira PE, Lunshof L, Odink RJ, Oostdijk W, Rotteveel J, Schroor EJ, Van Alfen AA, Van Leeuwen M, Van Pinxteren-Nagler E, Van Wieringen H, Vreuls RC, Zwaveling-Soonawala N, de Ridder MA, Hokken-Koelega AC. Eight years of growth hormone treatment in children with Prader-Willi syndrome: maintaining the positive effects. *J Clin Endocrinol Metab*. 2013;**98**(10):4013–4022.
13. Donze SH, Damen L, Mahabier EF, Hokken-Koelega ACS. Improved mental and motor development during 3 years of GH treatment in very young children weith Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2018;**103**(10):3714–3719.
14. Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Troeman ZC, van Alfen-van der Velden AA, Otten BJ, Rotteveel J, Odink RJ, Bindels-de Heus GC, van Leeuwen M, Haring DA, Oostdijk W, Bocca G, Mieke Houdijk EC, van Trotsenburg AS, Hoorweg-Nijman JJ, van Wieringen H, Vreuls RC, Jira PE, Schroor EJ, van Pinxteren-Nagler E, Willem Pilon J, Lunshof LB, Hokken-Koelega AC. Beneficial effects of growth hormone treatment on cognition in children with Prader-Willi syndrome: a randomized controlled trial and longitudinal study. *J Clin Endocrinol Metab*. 2012;**97**(7):2307–2314.
15. Lo ST, Festen DA, Tummers-de Lind van Wijngaarden RF, Collin PJ, Hokken-Koelega AC. Beneficial effects of long-term growth hormone treatment on adaptive functioning in infants with Prader-Willi syndrome. *Am J Intellect Dev Disabil*. 2015;**120**(4):315–327.
16. Carrel AL, Myers SE, Whitman BY, Eickhoff J, Allen DB. Long-term growth hormone therapy changes the natural history of body composition and motor function in children with prader-willi syndrome. *J Clin Endocrinol Metab*. 2010;**95**(3):1131–1136.
17. Tan HL, Urquhart DS. Respiratory Complications in Children with Prader Willi Syndrome. *Paediatr Respir Rev*. 2017;**22**:52–59.
18. Kuppens RJ, Bakker NE, Siemensma EP, Tummers-de Lind van Wijngaarden RF, Donze SH, Festen DA, van Alfen-van der Velden JA, Stijnen T, Hokken-Koelega AC. Beneficial effects of GH in young adults with Prader-Willi syndrome: a 2-year crossover trial. *J Clin Endocrinol Metab*. 2016;**101**(11):4110–4116.
19. Boot AM, Bouquet J, de Ridder MA, Krenning EP, de Muinck Keizer-Schrama SM. Determinants of body composition measured by dual-energy X-ray absorptiometry in Dutch children and adolescents. *Am J Clin Nutr*. 1997;**66**(2):232–238.
20. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res*. 2000;**47**(3):316–323.
21. Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. *Arch Dis Child*. 2000;**82**(2):107–112.
22. Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. Westchester, IL: American Academy of Sleep Medicine; 2007.
23. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien, IL; American Academy of Sleep Medicine; 2014.
24. Rikken B, van Doorn J, Ringeling A, Van den Brande JL, Massa G, Wit JM. Plasma levels of insulin-like growth factor (IGF)-I, IGF-II and IGF-binding protein-3 in the evaluation of childhood growth hormone deficiency. *Horm Res*. 1998;**50**(3):166–176.

25. Kuppens RJ, Bakker NE, Siemensma EP, Donze SH, Stijnen T, Hokken-Koelega AC. Metabolic health profile in young adults with Prader-Willi syndrome: results of a 2-year randomized, placebo-controlled, crossover GH trial. *Clin Endocrinol (Oxf)*. 2017;**86**(2):297–304.
26. Miller J, Silverstein J, Shuster J, Driscoll DJ, Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2006;**91**(2):413–417.
27. Al-Saleh S, Al-Naimi A, Hamilton J, Zweerink A, Iaboni A, Narang I. Longitudinal evaluation of sleep-disordered breathing in children with Prader-Willi syndrome during 2 years of growth hormone therapy. *J Pediatr*. 2013; **162**:263–268.
28. Khayat A, Narang I, Bin-Hasan S, Amin R, Al-Saleh S. Longitudinal evaluation of sleep disordered breathing in infants with Prader-Willi syndrome. *Arch Dis Child*. 2017;**102**(7):634–638.
29. Berini J, Spica Russotto V, Castelnuovo P, Di Candia S, Gargantini L, Grugni G, Iughetti L, Nespoli L, Nosetti L, Padoan G, Pilotta A, Trifirò G, Chiumello G, Salvatoni A; Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED). Growth hormone therapy and respiratory disorders: long-term follow-up in PWS children. *J Clin Endocrinol Metab*. 2013;**98**(9):E1516–E1523.
30. Cohen M, Hamilton J, Narang I. Clinically important age-related differences in sleep related disordered breathing in infants and children with Prader-Willi Syndrome. *PLoS One*. 2014;**9**(6):e101012.