Growth Hormone Therapy and Respiratory Disorders: Long-Term Follow-up in PWS Children

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Context: Adenotonsillar tissue hypertrophy and obstructive sleep apnea have been reported during short-term GH treatment in children with Prader-Willi syndrome (PWS).

Objective: We conducted an observational study to evaluate the effects of long-term GH therapy on sleep-disordered breathing and adenotonsillar hypertrophy in children with PWS.

Design: This was a longitudinal observational study.

Patients and Methods: We evaluated 75 children with genetically confirmed PWS, of whom 50 fulfilled the criteria and were admitted to our study. The patients were evaluated before treatment (t0), after 6 weeks (t1), after 6 months (t2), after 12 months (t3), and yearly (t4–t6) thereafter, for up to 4 years of GH therapy. The central apnea index, obstructive apnea hypopnea index (OAHI), respiratory disturbance index, and minimal blood oxygen saturation were evaluated overnight using polysomnography. We evaluated the adenotonsillar size using a flexible fiberoptic endoscope.

Results: The percentage of patients with an OAHI of >1 increased from 3 to 22, 36, and 38 at t1, t4, and t6, respectively ($\chi^2 = 12.2$; $P < .05$). We observed a decrease in the respiratory disturbance index from 1.4 (t0) to 0.8 (t3) ($P < .05$) and the central apnea index from 1.2 (t0) to 0.1 (t4) ($P < .0001$). We had to temporarily suspend treatment for 3 patients at t1, t4, and t5 because of severe obstructive sleep apnea. The percentage of patients with severe adenotonsillar hypertrophy was significantly higher at t4 and t5 than at t0. The OAHI directly correlated with the adenoid size (adjusted for age) ($P < .01$) but not with the tonsil size and IGF-1 levels.

Conclusion: Long-term GH treatment in patients with PWS is safe; however, we recommend annual polysomnography and adenotonsillar evaluation. (***J Clin Endocrinol Metab*** **98: E1516–E1523, 2013)**

Prader-Willi syndrome (PWS) is a rare genetic disease characterized by low birth weight, neonatal hypotonia, poor muscle development, inadequate suction, genital hypoplasia, small hands and feet, sticky saliva, short stature, temper tantrums, and mental retardation of variable degree (1). Children with PWS are at risk of morbid obe-

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Abbreviations: BIA, bioimpedance analysis; BMI, body mass index; CAI, central apnea index; ENT, otolaryngology; HOMA, homeostasis model assessment; OAHI, obstructive apnea hypopnea index; OSA, obstructive sleep apnea; POI score, Polisomnography-Otolaryngology-IGF1 score, PSG, polysomnography; PWS, Prader-Willi syndrome; RDI, respiratory disturbance index; t0–t6, time 0–6.

sity caused by excessive attraction to food and lack of satiety (2, 3). Central and obstructive sleep-disordered breathing, often reported in children with PWS (1, 4), causes poor sleep quality, excessive daytime sleepiness, and sedentary behavior with further increased risk of obesity (5, 6). Obstructive sleep apneas (OSAs) may depend not only on airway narrowing because of excessive fat but also on airway collapse caused by pharyngeal wall hypotonia and adenoid/tonsil hypertrophy (7). Additionally, the central disordered breathing has been demonstrated to be more severe in patients with PWS who exhibit hypothalamic/pituitary adrenal insufficiency during stress (8). Hypopituitarism due to hypothalamic dysfunction is well established in PWS; GH replacement treatment has been reported to be successful in promoting growth and improving muscular trophism and tone, with a consequent improvement in strength, agility, physical activity, and cardiorespiratory function (9–11). From 2002 to 2005, however, several cases of sudden death during the initial phase of GH treatment have been reported (12–21). Autopsy findings showed, in most cases, a significant increase in lymphatic tissues, in particular, the adenoids and tonsils, supporting the hypothesis that airway obstruction is the cause of death. Another possible explanation for the cardiorespiratory impairment and eventually death during GH treatment is that the antinatriuretic property of GH results in cardiac overload (22). Short-term GH administration has been demonstrated to stimulate the production of immune system cytokines (23); thus, adenotonsillar enlargement is also conceivable. Although in the last 7 years there have been no reported deaths in patients with PWS at the start of GH treatment, 2 reports have demonstrated that sleep-disordered breathing may occasionally occur in patients with PWS on long-term GH therapy (24, 25). In this article, we report the effect of GH treatment on breathing during sleep, body weight, adenotonsillar size, water retention, IGF-1, and insulin sensitivity in 50 children with PWS who were treated for up to 4 years.

Subjects and Methods

Subjects

Seventy-five children with PWS were consecutively enrolled in the Pediatric Unit of del Ponte Hospital in Varese from January 1, 2005, to December 31, 2010. The patients had been referred from other Italian centers for polysomnographic assessment before starting GH treatment. Thirty-three patients had a deletion of chromosome 15q11–13; 36 demonstrated maternal disomy of chromosome 15; and 6 showed only methylated DNA fragments. As recommended by the Consensus Guidelines for GH therapy in PWS (26), 25 patients who were markedly obese and/or had severe OSAs did not start GH therapy and were excluded from the study.

In accordance with the study design, the remaining 50 patients with PWS were assessed before GH treatment (t0), after 6 weeks (t1), 6 months (t2), and 12 months (t3) of treatment and yearly thereafter (t4–t6) for up to 4 years (see biographical data in Table 1). On December 31, 2012, 48 of 50 patients (96%) had completed 1 year, 22 of 50 (44%) completed 2 years, 12 of 50 (24%) completed 3 years, and 8 of 50 (16%) completed 4 years of GH treatment. All of the patients underwent biochemical and anthropometric evaluation, polysomnography (PSG) and otolaryngology (ENT) examinations. This study was approved by the local ethics committee. We obtained informed written consent from the patients' parents at t0.

Anthropometric evaluation

Supine length before the age of 2.5 years and height thereafter were measured to the nearest millimeter using a Harpenden stadiometer, and weight was measured to the nearest 100 g using a mechanical scale. Body mass index (BMI) was calculated according to the formula weight (kilograms)/height^2 (square meters) and expressed as *z*-score using World Health Organization standards (27, 28).

Intracellular water estimate

Intracellular water was evaluated using multifrequency bioimpedance analysis (BIA) (Human-IM Scan; Dietosystem). The ratio of impedance at 1 to 100 kHz was used as the index of intracellular water compartment extent (29).

Polysomnography

The PSG was performed using an e-Series PSG system (Compumedics), and the following channels were recorded: electroencephalographic leads (C3-A2, O2-A1, O1-A2), left and right electro-oculograms, submental electromyogram (using 2 electrodes located at the point of the chin and belly of the digastric muscle on each side of the chin), electrocardiogram, airflow by nasal pressure transducer (similar to a nasal cannula connected to a pressure transducer that provides a semiquantitative estimate of airflow based on pressure measurement), respiratory effort by thoracic and abdominal strain gauges, snoring noise by a microphone, arterial oxygen saturation using a pulse oximeter (Xpod model 3011; Nonin Medical Inc), and body position modification by a sensor. The American Academy of Sleep Medicine criteria were used for PSG evaluation (30). OSA was defined as a $\geq$90% drop in the signal amplitude of airflow for $\geq$90% of the entire event, compared with the pre-event baseline amplitude, and the final event for at least 2 breaths (or the duration of 2 baseline breaths) with continued inspiratory effort throughout the entire period of decreased airflow. The obstructive apnea index was defined as the number of OSAs per hour of total sleep time. Central apnea was scored if the respiratory event was associated with absent inspiratory effort throughout the duration of the event and if one of the following was present: the event lasted >20 seconds or the event lasted at least 2 missed breaths and was associated with an arousal, awakening, or a $\geq$3% desaturation. Central apnea index (CAI) was defined as the number of central apneas per hour of total sleep time. Central apneas occurring immediately after a sigh, movement or awakening were not included in the CAI.

Table 1. Auxological and Metabolic Findings Before and During GH Treatment in 50 Children With PWS[a]

	GH Therapy Duration, mo						
	0 (t0)	**1.5 (t1)**	**6 (t2)**	**12 (t3)**	**24 (t4)**	**36 (t5)**	**48 (t6)**
n	50	50	38	48	22	12	8
Gender (male/female)	24/26	24/26	23/15	23/25	9/13	8/4	5/3
Age, y	1.9	2.6	2.9	3.3	4.6	5.7	6.9
IQR	2.2	2.4	2.3	2.4	2.6	1.9	1.8
Interval	0.4–7.8	0.8–8.4	1.1–8.8	1.6–9.2	2.6–8.5	3.8–11.2	5.3–9.0
Length/height (z-score)	−1.8	−1.8	−1.6	−1.5[d]	−1.2[b]	−1.6[c]	−1.2
IQR	1.8	1.6	1.4	1.4	1.4	1.5	2.0
Interval	−4.3 to 0.4	−4.6 to 0.4	−4.3 to 0.3	−4.4 to 1.6	−3.3 to 0.8	−3.3 to 0.6	−2.1 to 0.5
BMI (z-score)	0.40	0.41	0.32	0.38	1.10	1.34	1.43
IQR	1.84	1.88	2.20	2.52	2.03	1.57	1.43
Interval	−2.7 to 2.9	−2.7 to 2.9	−1.8 to 3.0	−3.28 to 3.3	−1.7 to 2.9	−0.3 to 2.7	0.0–2.6
IGF-1 (z-score)	−0.81	0.48[c]	−0.07[d]	0.57[d]	1.23[d]	0.05	1.60[c]
IQR	1.95	1.85	1.12	1.20	1.52	2.06	0.78
Interval	−6.44 to 1.63	−2.49 to 4.07	−4.91 to 2.22	−1.75 to 4.23	−1.39 to 3.33	−1.80 to 1.50	0.23–2.58
HOMA	0.82	1.13[d]		1.07[b]			
IQR	0.33	1.06		1.19			
Interval	0.21–2.39	0.49–4.25		0.20–10.33			
BIA, 1 kHz/100 kHz	0.847	0.865	0.869	0.864	0.858	0.815	0.825
IQR	0.090	0.060	0.042	0.054	0.095	0.123	0.036
Interval	0.517–0.894	0.549–0.936	0.567–0.910	0.600–0.899	0.753–0.947	0.717–0.881	0.797–0.845

[a] The data are reported as the median along with interquartile range (IQR) and interval. Wilcoxon paired sign rank test was used to compare basal (t0) parameters with those collected at a different duration time of the GH treatment (t1–t6).

[b] $P < .05$.

[c] $P < .01$.

[d] $P < .001$.

Mixed apnea was defined as an apnea with both central and obstructive components. Mixed apneas were counted as obstructive apneas. Hypopnea was defined as a ≥50% drop in airflow signal amplitude compared with the pre-event baseline amplitude for at least 90% of the duration of the event. Hypopnea was characterized as obstructive if the reduction in airflow was associated with paradoxical chest and abdominal movement or central if associated with an in-phase reduction in the amplitude of chest and abdominal signals. The obstructive apnea hypopnea index (OAHI) (30) was defined as the total number of OSAs, mixed apneas, and obstructive hypopneas per hour of sleep.

The respiratory disturbance index (RDI) was defined as the sum of all apneas (obstructive, central, and mixed) per hour of total sleep time. The patients with an OAHI of ≥1 were considered to have pathological obstructive sleep (31).

ENT examination

An ENT examination of the upper airways was performed using a 2.4-mm FNL-7RP3 flexible fiberoptic endoscope (Pentax Medical Company) with topical anesthesia and video recording by 2 operators (P.C. and G.P.). Tonsil hypertrophy was scored from 0 to +4 (T0–T4) according to the Brodsky criteria (32); adenoid hypertrophy was classified as the proportion of airway patency reduction at vomer level into 4 categories (A0–A3) according to the criteria by Wang and colleagues (33). Moreover, the presence of acute or chronic inflammation was evaluated by physical examination and anamnestic investigation. The patients with acute upper airway inflammation received proper antibiotics and anti-inflammatory treatment; they were reevaluated before starting GH treatment.

Biochemical evaluation

Blood samples for biochemical tests were taken after an overnight fast. IGF-1 and insulin were measured in serum using an RIA technique (Bioclone Australia Pty Limited; Adaltis Italia SpA). The IGF-1 levels were standardized for age and gender by standard deviation score conversion (SDS) using the laboratory reference values. Blood glucose was measured in plasma using the hexokinase-glucose-6-phosphate dehydrogenase (HK GSPDH) method (Olympus America Inc). Insulin sensitivity was assessed by homeostasis model assessment (HOMA) (34).

GH treatment

The GH treatment was undertaken at a dosage ranging from 0.010 to 0.030 mg/kg/d. Both starting dosage and subsequent adjustments of the therapy have been established on the basis of a 15-point score (POI score, Polisomnography-Otolaryngology-IGF1 score) taking into account polysomnographic parameters (RDI), size of tonsils and adenoids, and IGF-1 levels (Table 2) (35). The predictive power of the POI score on adverse outcomes has not been established. However, we decided to use this tool to better standardize the modulation of the therapy.

Statistical analysis

The results are reported as the median, interquartile range (IQR), and interval. The sample size was sufficient to detect an OAHI, RDI, and POI score change exceeding 0.17, 1.4, and 1.6, respectively, with 95% confidence interval and >90% statistical power. The statistical analysis of the continuous values before and after GH treatment was performed using the nonparametric paired Wilcoxon sign rank test, Friedman test, and Kruskal-Wal-

Table 2. Summary of the Procedure for POI Score Calculation and the Advice on the Modulation of GH Therapy According to the Score Value[a]

	Values and Scores			
PSG				
Mean SpO_2, %	>97	>95	<95	
Score	0	1	2	
RDI	<1	1–3	3–5	>5
Score	0	2	3	4
Otorhinolaryngology				
Tonsils (degree), %	0–25	25–50	50–75	75–100
Score	0	1	2	3
Adenoids	<1/3	1/3	2/3	3/3
Score	0	1	2	3
IGF-1, percentile	<25th	25–50th	50–75th	>75th
Score	0	1	2	3
Score	Not yet on treatment		In treatment with GH	
0–3	Start full dose		Maintain or increase	
4–6	Start 1/2 dose		Maintain	
7–9	Start 1/3 dose		Decrease 50%	
≥10	No start		Stop therapy	

[a] Permission to republish no. 11090171 obtained by Hormone Research in Paediatrics) (35).

lis test. Fisher's exact test was used to compare the distribution of the noncontinuous values. Statistical significance was set at $P < .05$.

Results

Polysomnography

From t0 to t5, we observed an increase in the OAHI (Table 3). In particular, 11 of 50 patients (22%) showed an OAHI of >1 during the treatment. Three patients had to temporarily discontinue the GH treatment (at t1, t4, and t5) because of POI scores of >10, for periods ranging from 2 to 4 months. In two other patients, the GH treatment was discontinued and not resumed in accordance with parental request. Moreover, during the GH treatment, we observed a significant improvement in the RDI primarily due to a progressive decrease in the CAI over time (Table 3).

Table 3. Trend of Polysomnographic Parameters During GH Treatment in 50 Patients With PWS[a]

	Time, mo						
	0 (t0)	**1.5 (t1)**	**6 (t2)**	**12 (t3)**	**24 (t4)**	**36 (t5)**	**48 (t6)**
n	50	50	38	48	22	12	8
OAHI	0.1	0.4[b]	0.3	0.6[d]	0.5[c]	0.7	0.7
IQR	0.5	0.9	0.6	0.9	1.2	0.8	1.3
Interval	0–1.2	0–15.8	0–3.7	0–3.0	0–7.7	0–3.2	0–3.2
OAHI >1, n (%)	3 (6)[e]	11 (22)[e]	8 (21)[e]	10 (21)[e]	8 (36)[e]	4 (33)[e]	3 (38)[e]
CAI	1.2	0.6[c]	0.2[b]	0.1[d]	0.0[c]	0.0[d]	0.0
IQR	2.7	1.9	1.7	0.9	0.3	0.0	0.2
Interval	0–12.1	0–7.8	0–4.0	0–4.5	0–0.9	0–0.8	0–0.5
RDI	1.4	1.5	0.7	0.8[b]	0.6	0.7	0.8
IQR	2.4	2.2	1.9	1.2	1.3	0.8	1.4
Interval	0–12.5	0–15.9	0–6.6	0–4.5	0–8.6	0–4.0	0–3.8
$MinO_2$	88.0	86.5	85.0	86.2	83.5	87.0	85.0
IQR	6.5	9.0	9.0	12.0	12.0	14.5	8.5
Interval	71–94	60–94	55–94	67–97	53–94	59–95	78–97

Abbreviation: $MinO_2$, minimum value of blood oxygen saturation during polysomnography.

[a] Unless indicated otherwise, the data are reported as the median along with interquartile range (IQR) and interval. Wilcoxon paired sign rank test was used to compare basal (t0) parameters and those collected at a different duration of time of the GH treatment (t1–t6). Fisher's exact test was applied to compare the distribution of the noncontinuous values.

[b] $P < .05$.

[c] $P < .01$.

[d] $P < .001$.

[e] $\chi^2 = 12.2$; $P < .05$.

Otolaryngology

The ENT evaluation revealed a significant increase (+24% for adenoids and +15% for tonsils) in the percentage of patients showing more severe hypertrophy (stage A3 and T4) at t4 and t5 (Figure 1). Previously treated unsuccessfully with topical steroid, one patient required adenotonsillectomy at t3 and two patients at t5.

Because the adenotonsillar tissue in childhood changes in size with age, achieving on average the largest volume between 5 and 8 years (36), tonsil and adenoid scores were adjusted for age. The age-dependent component of adenotonsillar volume was obtained through a second-degree regression model (stage A = 0.742 + 0.358 age (years) − 0.039 age (years)^2, $R^2 = 0.107$, $P < .0001$; and stage T = 1.036 + 0.367 age (years) − 0.045 age (years)^2, $R^2 = 0.086$, $P < .0001$). The size of adenoids adjusted for age was significantly related to the OAHI (Figure 2).

Auxological evaluation and intracellular water estimate

During GH treatment, the BMI z-score and intracellular water compartment extent (estimated by BIA 1 kHz/100 kHz ratio) did not change significantly, whereas a significant increase was observed in height z-score, as determined by Wilcoxon sign rank paired test (Table 1).

IGF-1 and insulin sensitivity

During GH treatment, we observed a significant increase in the IGF-1 level, whereas insulin sensitivity evaluated by HOMA did not change (Table 1).

POI score

Although mean POI score, a decisional tool recently proposed for starting and adjusting GH therapy in children with PWS (35), did not change significantly during GH treatment, several patients showed a clear increase in POI values above the 90th percentile during treatment (Figure 3).

Discussion

Since 2000, GH has been registered by the U.S. Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products (now EMA, formerly EMEA) for use in PWS with and without GH deficiency. Although sudden deaths, caused by suspected airway obstruction, have been reported at the beginning (12–21), follow-up of subsequent multiple cases (9–11) and randomized placebo-controlled clinical studies (37, 38) have documented favorable effects of the treatment not only on stature but also on lean mass accretion, temper, and respiratory function. In a previous study performed during the first 6 weeks of treatment, we showed that the therapy is safe if it is initiated in lean children without OSA and with patent upper airways (39). The overall results of this 48-month follow-up study confirm that GH treatment, on average, does not impair respiratory function during sleep. In fact, during GH treatment, we observed a significant improvement in the RDI, primarily because of the progressive decrease in the CAI over time. The most evident

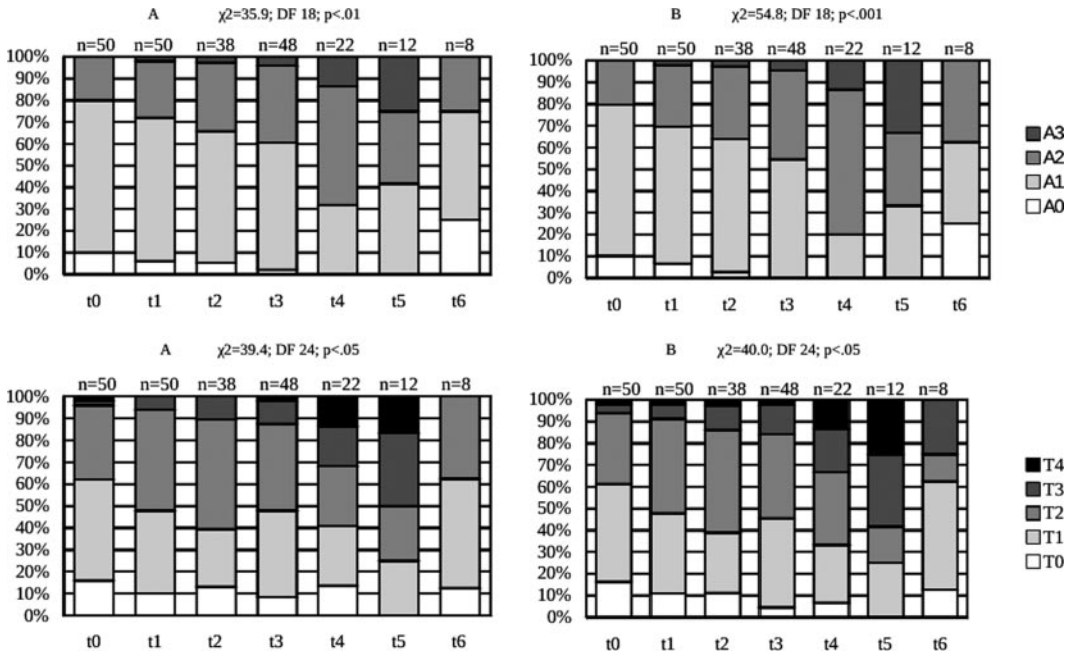

Figure 1. Trend of tonsil and adenoid hypertrophy during GH treatment in 50 patients with PWS. The histograms show a significant increase over time in the percentage of patients with adenoid (A0–A3) and tonsil (T0–T3) hypertrophy (staged according to Wang and Brodsky criteria) both before (A) and after (B) adjustment for age.

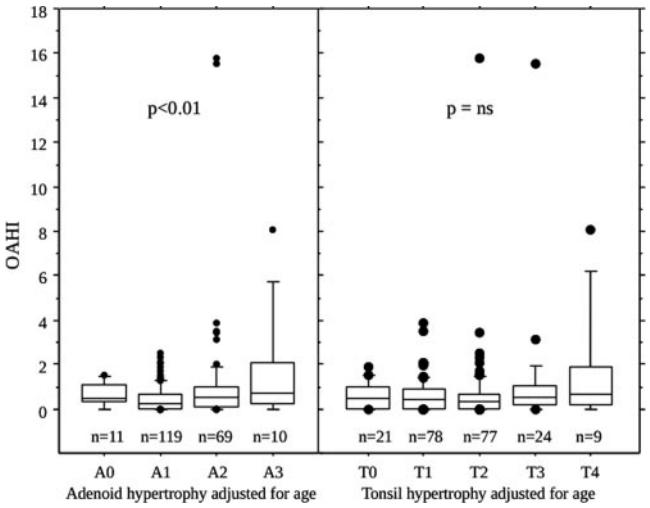

Figure 2. Box plot showing 10th, 25th, 50th (median), 75th, and 90th percentiles of OAHI values according to adenoid and tonsil size adjusted for age in 50 children with PWS before and during GH treatment. The Kruskal-Wallis test was used for statistical analysis. The graph shows a significant direct relationship between the extent of hypertrophy of the adenoids and the OAHI. A similar relationship was present for the tonsils but did not achieve statistical significance.

polysomnographic changes during GH treatment were the reduction of CAI and the increase of OAHI, the latter in lower proportion compared with the reduction of CAI, leading to a reduction of RDI achieving statistical significance at t3 (Table 3). RDI instead of OAHI was used in POI score for safety reasons, assuming that the association of OSA to CAI must be considered a major risk for severe adverse events. Because RDI accounts for both, it is, in our view, a more reliable risk index.

Because of the lack of a control group, a weakness in this study, we cannot conclude whether this improvement is attributable to GH therapy. A recent 2-year follow-up study on 15 children with PWS, selected with criteria close to those of our study, reached similar conclusions (25). Additionally, we did not observe an overall significant change in BMI, insulin sensitivity, or water retention, but we observed a significant increase in stature and IGF-1 levels.

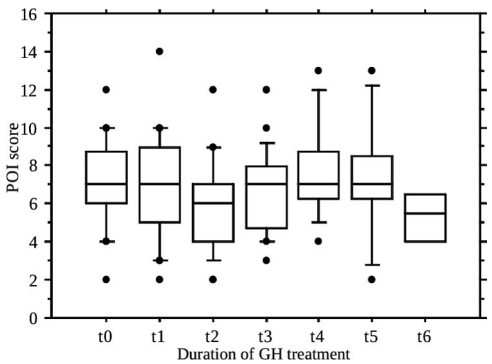

Figure 3. Trend of POI score (35) during GH treatment in 50 children with PWS. The box plots show the 10th, 25th, 50th (median), 75th, and 90th percentiles. The score provides a concise overview of polysomnographic, ENT, and endocrine (IGF-1) parameters. All values above the 90th percentile or below the 10th percentile are plotted separately. Both paired Friedman and unpaired Kruskal-Wallis tests did not achieve statistical significance.

The originality of our study lies in the large number and particular selection of patients (not severely obese and without OSA and adenotonsillar hypertrophy at the start of GH treatment) and in the prolonged observation time (up to 48 months). Moreover, our study aimed to determine whether treatment with GH could cause, not only worsen, preexisting hypertrophy of the tonsils and adenoids. We found a direct relationship between the OAHI and the age-adjusted adenoid size, showing a probable major causative role of adenoid hypertrophy in the pathogenesis of OSA. The lack of a control group is again the primary obstacle that prevents us from addressing the question of whether GH causes adenotonsillar enlargement. However, age-adjusted adenotonsillar volume was not correlated with standardized levels of IGF-1, making it doubtful that GH has a dose-dependent effect on adenotonsillar hypertrophy. It is, therefore, likely that other GH-independent factors are responsible for the adenotonsillar hypertrophy and OSAs in patients with PWS. In light of this, it is important to bear in mind that tonsils and adenoids undergo physiological hypertrophy during childhood, peaking between 5 and 8 years of age (36). It is, therefore, possible that in PWS patients who begin GH treatment within the first 3 to 4 years of life, the progressive adenotonsillar enlargement may be partially physiological and thus independent of GH treatment. However, because of the unpredictable occurrence of severe OSAs, even during long-term GH therapy, prolonged PSG and ENT follow-up must be recommended. Additionally, Meyer et al (40) showed that adenotonsillectomy in PWS can reduce mild to moderate OSAs but does not seem to reduce severe sleep obstructive and central apneas. Consequently, it would be appropriate to extend the ENT and PSG monitoring to all of the subjects with PWS, not just those who receive GH treatment.

In conclusion, the results of the present study show that children with PWS can safely receive long-term GH treatment; however, caution must be taken, particularly during the first months of therapy, to avoid the possible development or worsening of OSAs. The observation of adenotonsillar hypertrophy and OSAs in single patients even after 2 or more years of treatment suggests the importance of PSG and ENT monitoring at least every year for the entire duration of GH therapy.

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