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Sleep Disordered Breathing in Infants with Prader-Willi Syndrome During the First 6 Weeks of Growth Hormone Therapy: A Pilot Study

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Background: Sleep-related breathing disorders are common in individuals with Prader-Willi syndrome (PWS). The US Food and Drug Administration approved the use of growth hormone in PWS in 2000. Many infants with PWS are being started on growth hormone therapy, but no data exist on the respiratory effects of growth hormone treatment in this age group.

Study Objectives: To perform overnight polysomnographic studies to evaluate the effects of growth hormone on sleep-related breathing in infants with PWS.

Methods: Pilot study evaluating overnight polysomnography before and 6 weeks after initiation of growth hormone therapy at a dose of 1 mg/m^2 per day in 20 infants from 2 to 21 months of age with genetically confirmed PWS. Polysomnography results were analyzed for frequency and severity of obstructive and central apnea and hypopnea events and the overall apnea-hypopnea index.

Results: When data were analyzed for the total group, there were no significant changes in sleep-related disorders before and after institution of growth hormone therapy. However, 12 infants had an increase in the frequency of obstructive events associated with either upper respiratory infections or a diagnosis of gastroesophageal reflux at the second sleep study (after institution of growth hormone therapy). Resolution of these conditions was associated with normalization of polysomnography results on follow-up studies.

Conclusions: Overall, growth hormone therapy, per se, had no significant effect on sleep related-breathing disorders in infants with PWS. Infants with upper respiratory infections of gastroesophageal reflux may be at risk for developing more obstructive events after beginning growth hormone treatment. We recommend close monitoring of infants with PWS after they begin growth hormone therapy, especially when they have upper respiratory infections.

Keywords: Prader-Willi syndrome, sleep disordered breathing, growth hormone

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Prader-Willi syndrome (PWS) is characterized by hypotonia and failure to thrive in infancy, followed by weight gain and an increased appetite, obesity, short stature, and hypogonadism.[1] Individuals with PWS often have sleep-related breathing disorders, including hypoventilation, obstructive sleep apnea (OSA), central sleep apnea, and an abnormal arousal and ventilatory response to hypercapnia.[2-6] PWS is an imprinted condition with approximately 70% due to a de novo deletion in the paternally inherited chromosome 15 q11-q13 region, 25% from a maternal uniparental disomy of chromosome 15, and the remaining 5% from either microdeletions or epimutations of the imprinting center in the 15q11-q13 region (i.e. imprinting defects) .[1,7,8]

With increased physician awareness of PWS as a cause of neonatal hypotonia, and with the advent of DNA methylation testing for PWS, the mean age of diagnosis of PWS has decreased substantially.[7,8] Children are often diagnosed within the first few weeks to months of life.[9] Growth hormone (GH) therapy is now being prescribed for infants with PWS soon after diagnosis as the result of reports on the benefits of early GH treatment on mental development, motor development, muscle mass, and fat mass.[10-12]

The annual death rate of individuals with PWS is high (3%).[13] The most commonly identified causes of death in infants with PWS who are not on GH treatment are respiratory disorders (infection or insufficiency), milk aspiration, and diarrhea with dehydration.[14-16] Respiratory disorders are also the most common cause of death in GH-treated infants and young children with PWS.[14] Most deaths in GH-treated youngsters with PWS occur during the first 9 months after beginning GH therapy, with several having occurred in the first 8 to 12 weeks after therapy was begun.[14-16] As a result of these deaths, all somatropin products (GH) now carry a warning that states that GH is contraindicated in patients with PWS who are severely obese or have severe respiratory impairment. All GH products now state that "fatalities have been reported in patients with PWS who had one or more of the following: severe obesity,

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history of upper airway obstruction or sleep apnea, or unidentified respiratory infection." These warnings about possible risk factors associated with fatalities have prompted many endocrinologists to either refuse to treat or stop treating children with PWS. No causal association between GH treatment and sudden death in individuals with PWS has been identified, however. One hypothesis for the association between GH therapy and deaths during upper respiratory infections (URI) is that GH treatment may cause enlargement of the tonsils and adenoids, which would narrow the already small airway of children with PWS, making it difficult for the child to overcome nasal or upper airway obstruction.[16] Several studies have shown that long-term GH therapy improves sleep disordered breathing (SDB) in older children and adults with PWS, but the short-term effects of this treatment on SDB breathing in infants with PWS has not been investigated.

We and others have found that SDB can significantly worsen when upper respiratory tract infections (URI) occur soon after children and adults with PWS start GH therapy. Although most individuals can overcome nasal obstruction during a URI by increasing mouth breathing, infants with PWS may be at increased risk for developing sleep-related breathing disorders when they have URI because their generalized hypotonia includes weak respiratory muscles. Infants typically are primarily nasal breathers; therefore, it is possible that respiratory compromise might occur in an infant with PWS who has a URI with nasal congestion and blockage of the nasal airway.

We undertook this study to examine the hypotheses that treating infants who have PWS with GH would improve breathing during sleep but that URI occurring soon after beginning GH therapy could potentially exacerbate sleep-related breathing disorders in this population. We chose an interval of 6 weeks between sleep studies, coinciding with the initiation and first 6 weeks of GH therapy, because several of the deaths in children with PWS occurred in the first few months after beginning GH therapy; therefore, we wanted to identify any worsening of sleep apnea early in the treatment course so that this potential cause of death and treatment of the apnea could be pursued.

METHODS

This was a pilot study of 20 infants with genetically confirmed PWS. Polysomnography was performed in the sleep laboratory at the University of Florida (American Academy of Sleep Medicine accredited) using a procedure standardized for the study of all age groups. The infants were 2 to 21 months of age at the time of their first sleep study. Repeat sleep studies were done 6 weeks after starting GH therapy. Ten children had PWS due to paternal deletion of 15q11-q13, 9 had PWS due to maternal uniparental disomy of chromosome 15, and 1 had an imprinting defect. Infants were started on a dose of GH of 1 mg/m^2 per day. No dose adjustments were made during the time between the 2 sleep studies. Samples for serum insulin-like growth factor (IGF)-1 measurement were obtained at the time of each study (ARUP Laboratories, Salt Lake City, UT). This study was approved by the University of Florida IRB, and all of the parents signed informed consent.

All polysomnographic studies were evaluated by a single person, who is board certified in sleep medicine (MW). Monitoring included central and occipital electroencephalogram, right and left electrooculogram, chin electromyogram, electrocardiogram, nasal pressure, airflow, respiratory effort, oxygen saturation, end-tidal carbon dioxide, and leg electromyogram. Sleep was staged in 30-second epochs using the criteria established by the American Academy of Sleep Medicine.[17] Events were scored using standardized pediatric criteria published by the American Academy of Sleep Medicine. Apnea events were scored if nasal pressure or flow decreased by 90% from baseline for at least 2 respiratory cycles. Hypopneas were scored when flow decreased by 50% from baseline and was associated with a 3% oxygen desaturation or arousal. Events were scored as central in origin if the decrease in air flow or nasal pressure was associated with a 90% decrease in effort; otherwise, events were scored as obstructive. Arterial blood gas measurement was obtained for persistent hypoxemia (saturation < 90%) or persistent hypercarbia (end-tidal carbon dioxide > 50 torr) to correlate with peripheral saturation and end-tidal carbon dioxide monitoring. Apnea and hypopnea indexes were determined for total events as well as for central and obstructive events. Indexes were calculated by dividing the number of events by the number of minutes of sleep to standardize event numbers for different total sleep times.

Statistical Methods

All comparisons were made using rank methods. The primary statistical comparisons were changes after GH treatment minus pre-GH treatment by 1-sample Wilcoxon sign rank tests. Secondary comparisons of baseline parameters by subtype of PWS and by sex were conducted by Wilcoxon 2-sample tests. Finally, as an additional secondary analysis, baseline parameters were correlated to age using Spearman correlation. Because this was a pilot study, no attempt was made to control for study-wide error. All p values are 2 sided, and $p < 0.05$ is considered as statistically significant.

RESULTS

As a group, infants with PWS had no significant worsening or improvement of SDB after 6 weeks of GH therapy (Table 1). Overall, GH treatment caused minimal changes in the sleep-related parameters evaluated in this pilot study, with a median difference of less than 10 events per hour between the pre-GH and GH treatment studies. No significant differences were found in degree of SDB among the children with different genotypes of PWS or between the sexes (details not shown). Additionally, no relationship between serum IGF-1 levels and degree of SDB was found in these infants (Table 1). There was a tendency toward more central sleep apnea after beginning GH therapy in younger infants ($p = 0.05$). Most of these infants had only mild increases in central events, however, with no significant change in their overall AHI.

In all of the infants, the number of both central and obstructive events was greatest during rapid eye movement (REM) sleep. The nadir of oxygen saturation typically occurred during the apnea and hypopnea events that took place during REM sleep. GH treatment did not significantly alter the distribution of central events during the sleep cycle. However, those infants

Table 1—Patient Characteristics and Polysomnography Results

Patient # (genotype)	Age, mo.[a]	Sex	IGF-1[b]		Obstructive, #		Central, #		REM-AHI		NREM-AHI		Minimum Sao_2, %	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1 (UPD)	2	F	0	0	2	0	27	210	18.5	29.1	6.4	1.5	81	86
2 (Del)	3	M	0	0	38	55	0	0	5.8	7.8	0	1	82	65
3 (UPD)	3	F	0	0	0	0	2	10	0	1.3	0.3	2.1	96	88
4 (Del)	3	M	-1.75	0	117	197	84.3	26	32.8	38.6	13.8	17.2	86	84
5 (Del)	3	F	-2	-0.5	38	17	59	11	24.9	34.9	14.3	10.3	86	90
6 (UPD)	4	M	0	0	101	312	37	2	50.1	74.1	5.8	21.9	90	87
7 (Del)	4	M	-0.25	-0.25	57	46	72	80	20.2	24.1	12.5	12.6	78	78
8 (UPD)	4	F	0	1.5	10	2	11	15	3.7	5.6	1.8	1.8	95	86
9 (Del)	6	M	0	0	14	27	9	5	3.1	12.5	1.6	10	88	87
10 (Del)	6/	M	-0.5	-0.25	124	2332	37	15	4.6	29.9	0.4	1.8	71	78
11 (UPD)	7	F	-0.25	0	65	33	43	16	30.4	12.6	3.5	2.9	89	90
12 (UPD)	7	F	0	0.5	23	20	9	12	9.5	4.9	2.9	2.7	84	83
13(ID)	10	M	-0.25	1	21	27	20	12	14.8	17.3	2.7	1.1	89	94
14 (UPD)	10	F	-1	0	59	25	10	9	12.4	5.4	3.5	2	84	93
15 (Del)	11	M	-2	-2	0	70	2	19	3.5	45.4	0.4	12.9	93	81
16 (Del)	11	M	-2	0	31	1	11	30	16.4	18	5.6	4.1	83	78
17 (Del)	14	M	-1.5	0	5	1	20	19	12.1	8.8	1.7	-3.4	90	89
18 (UPD)	14	M	-0.5	0	2	1	22	12	15.7	17.6	0.2	2.4	86	87
19 (Del)	18	M	0	0.5	2	35	8	30	0.8	14.6	1.8	6.7	81	95
20 (Del)	21	F	0	0	7	23	20	9	12.2	11.8	1.2	2.3	87	91
Median			-0.5	-0.05	35.8	34.8	25.2	27.1	14.7	20.7	4.2	5.6	85.9	85.5
Median Δ						-1		2		6		0.05		-0.4
p Value						0.77		0.99		0.93		0.93		0.90

Abbreviations: Obstructive refers to the number of obstructive apneas + obstructive hypopneas; central, central apneas + central hypopneas; REM-AHI, the number of apneas and hypopneas per hour of rapid eye movement sleep; NREM-AHI, the number of apneas and hypopneas per hour of non-rapid eye movement sleep; Sao_2, minimum oxygen saturation.

[a]Age at the baseline polysomnographic study, before initiation of treatment with growth hormone (GH).

[b]Insulin growth factor (IGF)-1 standard deviation scores (SDS) from mean for age and sex before GH treatment (Pre) or 6 months after initiation of GH treatment (Post).

[c]Differences (Δ) are post-GH minus pre-GH. Negative values indicate improvement between first and second studies. Positive values indicate worsening of study after GH.

[d]The 2332 obstructive hypopneas per hour on the second study resolved with treatment for gastroesophageal reflux.

who had a decrease in obstructive events on GH therapy, with a difference of more than 10 events per hour between the 2 studies, had their greatest improvements during REM sleep (Table 1). Because the amount of REM sleep influences the overall AHI in this population, some of the infants had mild s in their total AHI because they spent more time in REM sleep after beginning GH therapy.

When the studies of each infant before and after GH therapy were evaluated individually, we found some trends in SDB occurring during the sleep study conducted 6 weeks after initiation of GH treatment. Five infants had substantial improvements in the number of obstructive events during the second sleep study, with a change of greater than 30 events per hour noted after beginning GH therapy (Table 1; patients 4, 11, 14, 16, and 19). Of note, none of these infants were ill at the time of either study. Only 1 of these families consented to a third study after another 6 months of GH therapy, the results of which did not differ from those of the second study (Patient 19; Table 2).

Five infants had more obstructive events after beginning GH therapy, with more than 50 obstructive events per hour recorded during the second sleep study (Table 1; patients 2, 6, 10, 12, and 15), whereas 7 others had slight increases in the number of obstructive events during the second sleep study. All of the infants who had an AHI 5 or more obstructive events per hour were assessed immediately by both an otolaryngologist and a gastroenterologist. Although none of the infants were ill or found to have any additional medical issues at evaluation immediately after the baseline sleep study, examination immediately after the second study identified 3 infants with nasal congestion due to a URI and concurrent adenotonsillar enlargement for age. Only 1 of these infants underwent tonsillectomy immediately. The remaining infants were treated symptomatically with consideration for surgery delayed until the children were older because of the otolaryngologists' concerns about regrowth of lymphoid tissue in such young children.

All of the infants were monitored at home using a pulse oximeter during the first 6 months of GH therapy. Six of the 20 individuals in this study (including the 3 who had adenotonsillar hypertrophy during URI in infancy) had desaturations below 90% recorded on multiple occasions on home pulse oximeter during times of nasal congestion and have subsequently undergone adenoidectomy. To date, 2 have undergone tonsillectomy due to continuing desaturations on home pulse oximetry with URI or nasal congestion after adenoidectomy. Five infants, thus far, have had repeat polysomnography after tonsillectomy or adenoidectomy (Table 2).

Three infants with the most severe increase in the number of obstructive hypopnea events (more than 100 events per hour)

Table 2—Follow-Up Results for Subjects Having a Third Polysomnography Study

Patient #	Intervention	IGF-1	Obstructive	Central Events	NREM-AHI	REM- AHI	Sao_2, %
6	GERD Tx/adenoidectomy	0	-50	3	-5.4	-2.1	81
12	Adenoidectomy	0.5	-44	-8	-22	-30	96
14	Adenoidectomy	0	-11	28	0	0	95
15	GERD Tx	-2	-36	-11	-7.6	-15.6	87
16	T&A	0	-10	0	0	0	91
18	T&A	0	-1	-7	-0.9	-8.4	91
19	None	0.5	1	-4	-0.8	-2	95

Data are shown as insulin growth factor (IGF)-1 standard deviation score (SDS), as compared with mean for age and sex, or change in the number of events between the second and third studies. Negative values indicate improvement between second and third studies. Positive values indicate worsening. Obstructive refers to the number of obstructive apneas + obstructive hypopneas; central, central apneas + central hypopneas; REM-AHI, the number of apneas and hypopneas per hour of rapid eye movement sleep; NREM-AHI, the number of apneas and hypopneas per hour of non-rapid eye movement sleep; Sao_2, minimum oxygen; GERD Tx, treatment of gastroesophageal reflux disease; T&A, adenotonsillectomy.

on the sleep study 6 weeks after beginning GH therapy were found to have gastroesophageal reflux disease (GERD), diagnosed by pH probe. All were appropriately treated by a pediatric gastroenterologist. Home pulse-oximeter monitoring found that 2 had no further episodes of desaturations recorded after treatment of GERD. One infant had continuing desaturations during URI despite maximum medication therapy for GERD, which necessitated admission to the hospital twice for oxygen (Patient 6; Table 2). After the second hospitalization, the infant underwent adenotonsillectomy despite the fact that the otolaryngologist expressed concerns about performing this surgery on an infant. After surgery, the infant had no further desaturations on home pulse oximeter, even during respiratory illness, and a the findings on the fourth sleep study were normal for the child's age. Of the other 2 infants with GERD, 1 family consented to follow-up polysomnography while the child was on treatment (Table 2; Patient 15), which showed improvement in the number of obstructive events, but abnormal electroencephalographic activity was noted during this study, which made sleep staging difficult to perform.

DISCUSSION

GH therapy is routinely being prescribed for infants with PWS. Parents of infants with PWS pursue treatment as soon as possible because of the widely publicized beneficial effects of GH. Improvement in body composition, acquisition of motor skills, and delay of weight gain have been noted when infants with PWS are treated with GH; thus, treatment is often begun as soon as the diagnosis of PWS is made.[10-12] Although we and others have noted that children with PWS need to be monitored closely for the development of SDB during URI, the results of this pilot study suggest that our threshold for monitoring infants with PWS during URI or nasal congestion should be even lower than for older children and adults.[3,4]

The potential for OSA to occur in infants increases with respiratory infection because mucociliary clearance of airway secretions is decreased and cough reflexes are suppressed during sleep, which, in combination with atonia of the upper airway during REM sleep, can lead to upper airway occlusion. Nasal breathing is obligatory in infants, but mouth breathing can occur if nasal obstruction exist.[18] However, the response of initiating mouth breathing due to nasal obstruction is slower to occur in infants[19] than in adults and may be even slower to occur in infants with PWS because of abnormalities in cortical development.[20] The length of the apnea episode in infants is associated with a drop in oxygen level. These drops are, on average, twice as great after an obstructive event than after a central event of the same duration.[18]

Five infants in this pilot study had substantial worsening of obstructive events after starting GH, with an increase of more than 50 events per hour during the second sleep study. Three had a URI at the time of the second study and were found to have increased tonsil or adenoid size on examination, and 2 subjects were found to have GERD after the second study. GERD is an important cause of nasal obstruction in infants, and nocturnal gastroesophageal reflux has been shown to result in a higher AHI during REM sleep in infants without PWS.[21] It is unclear why GERD would develop or worsen with GH therapy, even when it was not noted before GH treatment, but, in our pilot study, appropriate medical therapy of the GERD reduced the number of desaturation events.

URI in infants and children with PWS have been found to be a risk factor for sudden death.[14-16] Whether the cause of death is severe OSA or due to another etiology, such as central adrenal insufficiency, is currently unknown.[13] OSA is thought to be caused by a dynamic process of structural upper airway narrowing and abnormal upper airway muscle tone.[22] One hypothesis as to the relationship between OSA and GH treatment in individuals with PWS is that the GH therapy may cause tonsil or adenoid hypertrophy, which, in combination with a narrow hypotonic airway, could result in OSA.[16,23] Although it has traditionally been thought that infants do not get OSA secondary to adenotonsillar hypertrophy, studies have shown that hypertrophy of the tonsils and adenoids can cause OSA in infants.[22] Over time, 6 infants in this study required adenoidectomy, with 2 having subsequent tonsillectomy because of parental reports of continuing obstructive events with oxygen desaturation during URI. All had 4 to 6 episodes of URI per year. All have done well since surgery, and the parents have noted improved sleep during the night and decreased daytime fatigue in their children. Overnight polysomnography after the adenoidectomy confirmed improvement in SDB.

Given the results of this study, we propose that, for infants with PWS who are beginning GH treatment, there should be a low threshold for monitoring using a home pulse oximeter,[24, 25]

especially during times of URI or if there is any suspicion of GERD. On October 31, 2008, the Food and Drug Administration mandated safety changes for several somatropin products, stating that the package inserts must carry a warning that individuals with PWS treated with GH should be monitored for signs of respiratory tract infections, with an emphasis on early diagnosis and aggressive treatment. Additionally, the Food and Drug Administration warning states that GH treatment should be interrupted in patients with PWS showing any signs of upper airway obstruction. The results of our pilot study indicate that these warnings should be clearly communicated to families by endocrinologists prescribing GH treatment for infants with PWS.

We did not find any relationship between serum IGF-1 measurements and SDB in infants with PWS. High IGF-1 levels have been associated with tonsil and adenoid hypertrophy both in individuals with acromegaly and in individuals treated with recombinant IGF-1.[26, 27] None of the infants in this study had abnormal IGF-1 levels for age at the time of either study, so we were unable to determine if elevated serum IGF-1 levels might be associated with increased SDB in this population.

This study was limited by its cross-sectional nature and the limited number of subjects. Additionally, although the pulmonologist (coauthor MW) reads all of the sleep studies performed on infants and children at our institution, the degree of variability and reproducibility of overnight polysomnography in infants is unknown. Studying non-GH treated infants with PWS at baseline and 6 weeks later would have been beneficial, but all of the families refused to wait for 6 weeks to begin GH therapy and undergo additional sleep studies for the purposes of a research study. At the University of Florida, we follow approximately 50 children from around the United States who started GH therapy during infancy, but, for the purposes of this report and to maintain consistency in scoring and interpretation of polysomnography findings, we were able to include only those who had their sleep studies done at our institution. An additional limitation of this pilot study is that the length of time that infants with PWS are at risk for developing significant OSA during URI or with GERD is unknown, so it is unknown how long these children require close monitoring during sleep and whether additional sleep studies are needed routinely after beginning GH therapy. This issue will need to be more closely investigated in future studies to determine the safest course of treatment for infants with PWS on GH therapy.

Although this was a purely observational study, the strength of which lies in the fact that the data were available to perform an analysis in a reasonable period, it should be seen as motivating future research to help assess the causality of the associations uncovered. The results of this pilot study suggest that development of a URI or GERD during the first 6 months of GH treatment can worsen sleep-related breathing problems in infants with PWS. It is hypothesized that the initiation of GH treatment could cause enlargement of the tonsils and adenoids, which, in combination with nasal obstruction from URI or GERD, could result in blockage of the narrow airway.[16, 23] We have been routinely monitoring all infants with PWS on GH therapy with home pulse oximetry and have advised the patients' parents to monitor their children closely during times of URI. If oxygen desaturations occur in the absence of URI symptoms, we recommend immediate referral for evaluation for GERD. Because of the many benefits that GH therapy offers these youngsters, we do not withhold treatment based on the polysomnography results, but we are aggressive about identifying and treating other potential causes of SDB, including URI, nasal congestion, GERD, and seizure disorders. Further prospective studies are planned to evaluate whether these findings are maintained during continued GH therapy or if the exacerbation of SDB occurs only with the initiation of GH treatment.

The optimal age for beginning GH therapy in individuals with PWS has yet to be determined, but, in this study, we found that infants with URI or GERD during GH treatment can have more obstructive events than have been noted in older children and adults in previously conducted studies.[3,4] Many of the infants we follow from other states have not had sleep studies because their local endocrinologists have been reluctant to put the infants through this test. However, if infants with PWS are going to be routinely treated with GH therapy, as is currently being done in the United States, we need more stringent criteria for monitoring the effects of the treatment and more thorough evaluations for other conditions, such as GERD, that could exacerbate SDB in these individuals. Our recommendation, after reviewing the results of our pilot studies in individuals of all ages with PWS, is that overnight polysomnography be done before and 6 weeks after starting GH therapy, as well as during any episodes of clinical sleep apnea, increased nighttime awakenings, or increased daytime sleepiness, and that, when they have a URI, infants with PWS should be monitored closely for the presence of OSA.

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