Short-Term Effects of Growth Hormone on Sleep Abnormalities in Prader-Willi Syndrome

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Context: GH was approved for Prader-Willi Syndrome (PWS) in 2000. Fatalities in individuals with PWS soon after beginning GH treatment prompted concern about GH worsening sleep apnea.

Objective: We sought to determine whether GH affects sleep apnea in individuals with PWS.

Design: Twenty-five patients with PWS had overnight polysomnography (PSA) at baseline and 6 wk after starting GH.

Setting: The study was conducted in a sleep lab using a standardized procedure.

Patients: The patients studied had genetically confirmed PWS.

Main Outcome Measures: PSA results were analyzed for frequency and severity of central and obstructive apnea/hypopnea events and total apnea/hypopnea index.

Results: As a group, GH improved apnea/hypopnea index by a mean of 1.2 events per hour (P = 0.02) and central events by a median of 1.7 events per hour (P = 0.001). Fourteen patients had improvement in obstructive events by a mean of 1.7 events per hour. Six patients had worsening of obstructive events on GH. Four of these patients had upper respiratory tract infections at the time of the second PSA and had tonsil/adenoid hypertrophy on otorhinolaryngological evaluation. Two patients with high serum IGF-I levels had increased obstructive events.

Conclusions: Most of our PWS patients had improvement after short-term GH treatment, but 32% had worsening of sleep disturbance. A subset of PWS patients are at risk during this window of vulnerability shortly after initiation of GH. Because it is difficult to predict who will worsen with GH, patients with PWS should have PSA before and after starting GH and should be monitored for sleep apnea with upper respiratory tract infections. Otorhinolaryngological evaluation is warranted if sleep apnea worsens on GH. IGF-I levels should be monitored, with the goal being physiological levels. (J Clin Endocrinol Metab 91: 413–417, 2006)

IN 2000, AN INTERNATIONAL group of pediatric endocrinologists agreed that medical evidence indicates that dysregulation of the GH/IGF axis is nearly universal in children with Prader-Willi syndrome (PWS), and thus, these patients should be offered GH treatment (1). The U.S. Food and Drug Administration approved the use of GH in individuals with PWS in 2000. GH therapy for PWS individuals has dramatic effects, including an increase in linear growth, muscle mass, and fat utilization as well as a decrease in total body fat (2–5). The greatest changes occur during the first 12 months of GH therapy (4, 6).

Individuals with PWS are known to have sleep-disordered breathing, including obstructive sleep apnea (OSA), central sleep apnea (CSA), abnormal arousals, abnormal circadian rhythm of rapid eye movement (REM) sleep with reduced REM latency, and abnormal cardiorespiratory response to hypercapnia (7). Sleep apnea occurs in 50–100% of individuals with PWS, although many studies have shown that the breathing abnormalities during sleep are mild (8–10). The cause of OSA in this population is thought to be a result of a combination of pharyngeal narrowing and respiratory muscle hypotonia (10, 11). Underlying restrictive lung disease caused by respiratory muscle weakness and scoliosis is also a risk factor for sleep-related hypoventilation and hypoxemia (7). Hypothalamic dysfunction is thought to be the cause of the CSA in light of the common findings in PWS of hypogonadism, temperature instability, appetite dysregulation, GH insufficiency, and abnormal response to hypercarbia in conjunction with the dysregulation of REM sleep that occurs in this syndrome (7). However, CSA is seen in non-PWS adults with GH deficiency after cessation of GH replacement, suggesting that the GH deficiency in PWS contributes to CSA (13). The hypothalamic dysfunction is also thought to cause reduced or absent hypoxic and hyperoxic ventilatory responses in individuals with PWS (14). Studies have shown that obesity in PWS can worsen the central apnea by further blunting the intrinsically abnormal ventilatory response to high levels of CO2 (13). Treatment of PWS patients with GH improves CSA and increases the respiratory response to hypercarbia during sleep after 6 months of therapy (8, 15). Reports of fatalities in individuals with PWS soon after starting GH treatment, however, prompted concern that GH might increase the risk of OSA (16–20).

Review of the reported cases of fatalities in patients with PWS on GH treatment revealed that most of those who died after starting GH therapy were morbidly obese at the time of death (9). All of the fatalities took place during the first 7
months of GH treatment, with most occurring in the first 3 months of therapy (9). Fatalities were caused by infection (17 of 22) and sleep apnea or hypoventilation (five of 22) (9). Although it is uncertain whether the deaths were related to GH therapy, two mechanisms are postulated. One is that increased OSA is a result of IGF-I-mediated hypertrophy of the tonsillar/adenoid tissue (21), and the other is that GH worsens preexisting impaired respiration by augmenting volume load (22) because short-term GH therapy can cause sodium retention with secondary water retention caused by an inappropriate increase in plasma renin activity that resolves with longer-term administration of GH (23, 24). More frequent episodes of OSA have been reported in a few GH-treated, non-PWS individuals (13). To date, no studies have evaluated whether sleep-disordered breathing changes in patients during the first few months of GH treatment. Therefore, we sought to determine whether GH therapy increased the incidence of OSA or any other sleep abnormalities in individuals with PWS, thus making them more susceptible to sudden death in the early phases of treatment.

### Subjects and Methods

#### Subjects

We evaluated patients with PWS who were either naive to GH therapy or who agreed to stop GH for 3 months and have a baseline sleep study obtained before restarting GH treatment. All patients were genetically proven to have GH by standard molecular testing (25). Patients were started on a standardized dose of GH (0.24 mg/kg-wk for children and 0.0006 mg/kg-d for adults) based on ideal body weight.

Seventeen PWS patients with a deletion of chromosome 15q11-13 region and eight patients with maternal uniparental disomy of chromosome 15, ages 6 months to 39 yr, underwent polysomnography off GH and again 6 wk after starting GH therapy. Two of these patients agreed to have repeat polysomnography done after 6 months of GH treatment. This study was approved by the Institutional Review Board at the University of Florida, and informed consent was obtained from patients, parents, or guardians.

#### Methods

Polysomnography was performed in a sleep laboratory using a standardized procedure. All studies were evaluated by a single person, board-certified in sleep medicine. Monitoring included central and cephalic electroencephalogram, electrooculogram, chin electromyogram, electrocardiogram, nasal pressure, airflow, respiratory effort, oxygen saturation, end tidal carbon dioxide (ETCO$_2$), and leg electromyogram. Sleep was staged in 30-sec epochs using Rechtschaffen and Kales criteria (26). Apnea events were scored if nasal pressure or flow decreased by 80% from baseline for at least two respiratory cycles. Hypopneas were scored when flow decreased by less than 80% from baseline and were associated with 3% oxygen desaturation, 3 torr increase in ETCO$_2$, or arousal. Events were scored as central in origin if the decrease in nasal flow/presure was associated with an 80% decrease in effort. Otherwise, events were scored as obstructive. Arterial blood gas was obtained for persistent hypoxemia (saturation < 90%) or persistent hypercapnia (ETCO$_2$ > 50 torr) to correlate with peripheral saturation and ETCO$_2$ monitoring. Apnea and hypopnea indices were determined for total events as well as central index (CI) vs. obstructive index (OI) events. Indices are calculated by dividing the number of events by the hours of sleep to standardize event numbers for different total sleep times.

All patients underwent a complete physical examination and had an IGF-I serum level measured at the time of initiation of GH treatment and on the day of their second sleep study, which occurred 6 wk after the start of GH therapy. During the examination, which took place before the sleep study, they were asked about concurrent symptoms, such as upper respiratory tract infection (URI) symptoms, headaches, leg/hip pain, polyuria/polydipsia, and abdominal pain.

### Statistical analysis

Two-sided nonparametric tests were used throughout. Changes in sleep-disordered breathing before compared with after GH treatment were tested by the Wilcoxon sign rank test. The Spearman rank correlation analysis was used to compare changes in apnea/hypopnea index (AHI), both overall and during REM sleep and obstructive and central events, with age and change in body mass index (BMI) sd score (SDS). The Wilcoxon rank sum test was used to assess differences in the AHI and the number of obstructive and central events or apneas per hour among age groups before and after 6 wk of GH treatment.

### Results

All 25 patients with PWS had sleep-disordered breathing during the baseline sleep study, including both obstructive and central events. The AHI increased during REM sleep in all patients. After 6 wk of GH treatment, 19 patients had improvement of the AHI, both overall (median improvement = −1.2 events per hour; P = 0.02) and during REM sleep (median = −2.9 events; P = 0.08) (Table 1). The frequency of central events also improved on GH therapy (CI median improvement = −1.7 events per hour; P < 0.001). The overall frequency of obstructive events did not significantly change (OI median improvement = −1.7 events per hour; P = 0.20). There was no difference in response of sleep-disordered breathing to GH treatment between the molecular subtypes. After 6 months of GH therapy, both patients who underwent repeat sleep studies had improvement in AHI from baseline (Table 2).

Six patients had worsening of OSA/hypopnea while receiving GH (Table 1). Four of these patients had concurrent URI as reported by their parents and confirmed by physical examination. All four were in school or daycare (age 6 months to 10 yr) and had multiple episodes of URI symptoms. All four had enlarged tonsils on otorhinolaryngological evaluation and subsequently underwent tonsillectomy and adenoidectomy, which clinically improved the symptoms of OSA. Two additional patients (ages 18 months and 3 yr) had initial improvement in their AHI during the sleep study (Table 1) but upon starting daycare developed URI, began to snore, and had brief periods of apnea described by their parents. Both of these patients had otorhinolaryngological examination and were found to have tonsillar hypertrophy. The parents refused another sleep study, opting for immediate adenotonsillectomy. All of the patients who underwent adenotonsillectomy for sleep apnea had clinical improvement, but none consented to a repeat sleep study after the procedure.

Two patients with worsening of obstructive events on GH therapy had a high serum IGF-I level for bone age at the time of the second sleep study (patients 22 and 24; Table 1). Their dose of GH was decreased to normalize circulating IGF-I concentrations. Repeat sleep studies after the IGF-I level was physiological revealed improvement in the AHI in one patient, with a decrease in the frequency and severity of obstructive events. However, the other patient had an increased AHI on the third sleep study with an increased number of obstructive events. This patient had a URI at the time of the third sleep study, was found to have tonsillar hypertrophy, and underwent an adenotonsillectomy. None of the parents of the patients who underwent adenotonsillectomy con-
TABLE 1. Patients with polysomnographic improvement and worsening of sleep-disordered breathing after 6 wk on GH

<table>
<thead>
<tr>
<th>Patient no. (genotype)</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>BMI SDSa</th>
<th>URI</th>
<th>Tonsillar hypertrophy</th>
<th>IGF-I SDS from mean for age/gender</th>
<th>Change in AHI</th>
<th>Change in REM AHI</th>
<th>Change in OI</th>
<th>Change in CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (UPD)</td>
<td>0.7</td>
<td>M</td>
<td>0</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-0.1</td>
<td>-3.3</td>
<td>-2</td>
<td>-8</td>
</tr>
<tr>
<td>2 (Del)</td>
<td>1.6</td>
<td>F</td>
<td>0</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-6.0</td>
<td>-0.4</td>
<td>0</td>
<td>-11</td>
</tr>
<tr>
<td>3 (Del)</td>
<td>1.6</td>
<td>F</td>
<td>0</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-0.4</td>
<td>-0.4</td>
<td>-3.4</td>
<td>0</td>
</tr>
<tr>
<td>4 (Del)</td>
<td>1.6</td>
<td>M</td>
<td>1.67</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-26.7</td>
<td>-3.3</td>
<td>0</td>
<td>-66</td>
</tr>
<tr>
<td>5 (Del)</td>
<td>2</td>
<td>F</td>
<td>0</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-0.6</td>
<td>-0.4</td>
<td>0</td>
<td>-11</td>
</tr>
<tr>
<td>6 (UPD)</td>
<td>3</td>
<td>M</td>
<td>3.3</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-1.2</td>
<td>-38.2</td>
<td>-0.1</td>
<td>-0.5</td>
</tr>
<tr>
<td>7 (Del)</td>
<td>3</td>
<td>M</td>
<td>10.5</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-0.9</td>
<td>-2.9</td>
<td>3</td>
<td>-21</td>
</tr>
<tr>
<td>8 (UPD)</td>
<td>8</td>
<td>M</td>
<td>8</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-7.3</td>
<td>-4.2</td>
<td>-21</td>
<td>-6.4</td>
</tr>
<tr>
<td>9 (Del)</td>
<td>12</td>
<td>F</td>
<td>1</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>+1</td>
<td>-2.3</td>
<td>-2.7</td>
<td>-5</td>
</tr>
<tr>
<td>10 (Del)</td>
<td>13</td>
<td>M</td>
<td>3.6</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>+1</td>
<td>-4.9</td>
<td>-5.9</td>
<td>-2.3</td>
</tr>
<tr>
<td>11 (Del)</td>
<td>18</td>
<td>M</td>
<td>4</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>0</td>
<td>-28.4</td>
<td>-26.4</td>
<td>-1.7</td>
</tr>
<tr>
<td>12 (Del)</td>
<td>19</td>
<td>M</td>
<td>2.95</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-1.3</td>
<td>-2.8</td>
<td>-2</td>
<td>-0.7</td>
</tr>
<tr>
<td>13 (Del)</td>
<td>21</td>
<td>M</td>
<td>2.5</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-12.1</td>
<td>-1.3</td>
<td>-66</td>
<td>-16</td>
</tr>
<tr>
<td>14 (Del)</td>
<td>21</td>
<td>F</td>
<td>0</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-13.5</td>
<td>-18.4</td>
<td>-3</td>
<td>-1.7</td>
</tr>
<tr>
<td>15 (UPD)</td>
<td>22</td>
<td>F</td>
<td>0.5</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-2.1</td>
<td>-40.9</td>
<td>-3</td>
<td>-0.9</td>
</tr>
<tr>
<td>16 (Del)</td>
<td>22</td>
<td>M</td>
<td>4</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-11.9</td>
<td>-2.3</td>
<td>-11.2</td>
<td>-0.2</td>
</tr>
<tr>
<td>17 (UPD)</td>
<td>23</td>
<td>M</td>
<td>0</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-1</td>
<td>-1.1</td>
<td>-3.1</td>
<td>0</td>
</tr>
<tr>
<td>18 (Del)</td>
<td>32</td>
<td>M</td>
<td>1.28</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-4.3</td>
<td>-7.1</td>
<td>-4.7</td>
<td>-6.4</td>
</tr>
<tr>
<td>19 (UPD)</td>
<td>34</td>
<td>F</td>
<td>3.1</td>
<td>/-</td>
<td>/-</td>
<td>0</td>
<td>-1.2</td>
<td>-5.8</td>
<td>-2.5</td>
<td>-1.3</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.023</td>
<td>0.082</td>
<td>0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OI is (obstructive apnea + obstructive hypopnea events)/hours of sleep, CI is (central apnea + central hypopnea events)/hours of sleep, and AHI is overall assessment of sleep-disordered breathing. Negative values indicate improvement from first to second sleep study. M, Male; F, female; Del, deletion of paternal chromosome 15q11–13; UPD, maternal uniparental disomy. /-/-, Absent at both sleep studies; /-/-, absent at first sleep study and present at second sleep study; /-/-/+, absent at first and second sleep study and present at third sleep study (patient with three sleep studies).

a BMI SDS before GH treatment.
b Patients who had development of OSA symptoms after sleep study.
c Patients with documented URI/adenotonsillar hypertrophy at time of follow-up sleep study.
d Patients with an elevated serum IGF-I concentration.

sent to a follow-up sleep study to document whether the procedure improved the sleep-disordered breathing.

There was no relationship in our study between change in AHI associated with GH treatment and BMI (P = 0.25). Ten patients had a BMI greater than 95% for age at the time of initial evaluation, with one of those being severely obese (>300% of ideal body weight for height). Seven of the most obese patients had a decrease in AHI during GH treatment (Table 1). The other three severely obese patients had worsening of their AHI, but had documented URI symptoms at the time of the second sleep study (Table 1). Five patients had weight gain during the first 6 wk of GH therapy, with worsening of their BMI, but none had worsening of their AHI.

Five of 11 patients aged 2–18 yr had worsening of their AHI in the first 6 wk of their GH treatment, whereas only one patient under age 2 yr had a decrease in AHI with GH therapy, and seven of eight adults (>21 yr of age) had improvement in AHI on GH. The one child under age 2 yr who had worsening of the AHI during the sleep study on GH was in daycare and had a documented URI at the time of the second sleep study, whereas the one adult who had an increase in AHI on GH had underlying respiratory problems. Overall, GH tended to improve AHI (mean, -6.8 ± 9.4; P = 0.08), obstructive events (OI mean, -6.1 ± 16.3; P = 0.05), and central events (CI mean, -8.7 ± 16.1; P = 0.07) in those who were either under age 2 or over age 18 yr compared with those individuals between ages 2 and 18 yr (AHI mean, 4.2 ± 13.4; OI mean, 3.8 ± 8.5; CI mean, -2.8 ± 7.4).

TABLE 2. Change in sleep disturbance from baseline after 6 months on GH treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Change in AHI</th>
<th>Change in REM AHI</th>
<th>Change in no. of obstructive events</th>
<th>Change in no. of central events</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>17</td>
<td>-13.3</td>
<td>-82.6</td>
<td>-19.8</td>
<td>-0.6</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>-17.7</td>
<td>-7.0</td>
<td>0</td>
<td>-3.1</td>
</tr>
</tbody>
</table>

Discussion

Most of our patients with PWS had improvement in sleep-disordered breathing after 6 wk of GH treatment. However, there was a subset that initially got worse in this short interval. Both patients who underwent repeat polysomnography after 6 months on GH had a decrease in AHI, which is consistent with previously published results (8). Overall, six patients had an increase in AHI on GH in the first 6 wk of treatment because of an increase in obstructive events likely related to chronic URI and inflammation in the upper airways. Additionally, one patient with underlying respiratory problems had worsening of obstructive events on
GH and had to be taken off of GH permanently. These findings underscore the recommendations originally put forth by Pharmacia/Pfizer and later endorsed by other GH manufacturers that GH should not be used in patients with chronic respiratory or lung infections (27). The recommendation also states that GH should not be used in patients with PWS who are severely obese. Three of our most obese patients had worsening of AHI on GH, but all were associated with URI symptoms. The most severe worsening of sleep-disordered breathing was seen in the most obese patient who had a concurrent URI, suggesting that the combination of severe obesity and upper airway inflammation could potentially have a tragic outcome.

Those patients with increased AHI associated with URI symptoms were between the ages of 6 months and 10 yr (five were under age 5), were attending school or daycare, and had recurrent URI. Studies investigating fatalities in PWS found that children not taking GH who died spontaneously had an average age of 2 yr compared with those who died while on GH, who were an average age of 4 yr (9). Although this finding could be a result of recruitment bias because GH is not approved for children with PWS under age 2 yr, it also could be a result of increased OSA in older toddlers from the combination of URI symptoms and GH. Our patients with URI symptoms and worsened sleep-disordered breathing were all found to have tonsillar/adenoid hypertrophy and underwent tonsillectomy/adenoidectomy. It should be noted that anesthesia carries significant risks in patients with PWS because of hypotonia and concurrent obesity (28).

The finding that two patients with a high IGF-I had worsening in OSA lends credence to the hypothesis that IGF-I-mediated tonsillar/adenoid hypertrophy may play a role in fatalities in children with PWS early in the course of their treatment with GH. Therefore, we recommend monitoring serum IGF-I concentration soon after starting GH and evaluation of tonsillar and adenoid size before and during treatment.

Causes of death in patients with PWS have not been well characterized, because autopsy is performed in a minority of cases (17). However, a recent study evaluating causes of death in patients with PWS, both with and without GH treatment, found that infants most commonly die of asphyxiation or hypothalamic dysregulation of respiration with hypoventilation, whereas adults most commonly die of complications related to morbid obesity (12). This study also found that sudden death in children and adolescents occurred most commonly during sleep in association with preceding viral infections, regardless of GH therapy (12).

Overall, we found that GH treatment improves the sleep-disordered breathing in the majority of patients with PWS but that a subset had worsening 6 wk after starting GH. Those who worsened had frequent respiratory infections, underlying respiratory problems, and a high serum IGF-I concentration on GH. These individuals require an otorhinolaryngological evaluation, consideration of adenotonsillectomy, and a decrease in GH, where appropriate, to normalize serum IGF-I levels. We recommend polysomnography at baseline and 6 wk after starting GH therapy in all patients with PWS, because there is a subset of patients with PWS who have worsening of sleep-disordered breathing during this vulnerable window of time after the initiation of GH therapy. Additionally, patients who develop symptoms of sleep apnea or snoring, regardless of how long they have been receiving GH, should have a sleep study and an otorhinolaryngological evaluation to ascertain that they have not had worsening of OSA. Individuals with PWS who have underlying chronic respiratory conditions probably should not receive GH treatment.

Acknowledgments

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