Outcomes of Adenotonsillectomy in Patients With Prader-Willi Syndrome

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Objective: To assess the efficacy of upper airway surgical intervention in patients with Prader-Willi syndrome (PWS). Due to reports of sudden death in children undergoing treatment with growth hormone for PWS, detection of sleep-disordered breathing by polysomnography (PSG) has been recommended.

Design: Retrospective study.

Setting: Multidisciplinary PWS Center at a tertiary care children’s hospital.

Patients: Thirteen pediatric patients with PWS who underwent adenotonsillectomy (T&A) with pre-PSG and post-PSG.

Main Outcome Measures: Comparison of PSG results before and after T&A.

Results: Six of our patients were girls (46%); 8 had genetic characteristics consistent with deletion (61%), and the remaining 5 had genetic characteristics consistent with uniparental disomy (39%). The median age at T&A was 3 years (age range, 6 months to 11 years), and the median age at start of growth hormone treatment was 8.5 months (range, 2 months to 6 years). Nine of the 13 patients had mild to moderate obstructive sleep apnea (OSA) or obstructive hypoventilation (69%); in 8 of these 9, breathing normalized after T&A. Four children had severe OSA prior to surgery (31%). Breathing normalized in 2 of these after surgery, but 2 had PSG findings of residual combined obstructive and central apneas postoperatively.

Conclusions: Adenotonsillectomy, while effective in most children with PWS who demonstrate mild to moderate OSA, may not be curative in children with severe OSA. An increase in central apneas can occur in some children with PWS postoperatively, and it is important to repeat PSG after surgery. Further studies are necessary to determine optimal treatment for some children with PWS and sleep-disordered breathing.
of these patients undergoing GH therapy at the time of death. Since these events, increased monitoring has been recommended in GH-treated patients with PWS specifically during sleep.

Patients with PWS are at risk for sleep-disordered breathing with central and obstructive components. Central sleep-disordered breathing is likely a result of hypothalamic dysfunction seen in PWS. This population has also been found to have decreased hypoxic ventilatory drive independent of obesity, and when obese, these patients have an added blunting of chemoreceptor responsiveness to hypercapnea. In addition, patients with PWS may have abnormal arousal to hypoxic events. Obstructive sleep-disordered breathing is multifactorial and related to poor muscle tone in the upper and lower airway, obesity, and adenoid and/or tonsil hypertrophy. Growth hormone therapy can contribute to obstructive sleep-disordered breathing as a known cause of tonsillar and adenoid hypertrophy in patients with and without PWS.

In 2008, consensus guidelines for the treatment of PWS were released that addressed the use of GH in this population. An international group of experts concluded that GH treatment was beneficial for patients with PWS as early as age 2 years, with growing evidence of additional benefit when administered at a younger age. These consensus guidelines suggested otolaryngology assessment and polysomnography (PSG) within the first 6 months of GH therapy to address the concerns of apnea in these at-risk patients. Further monitoring with PSG and otolaryngology evaluation were recommended if evidence of sleep-disordered breathing developed or worsened. Owing to insufficient data, no recommendations for routine monitoring with PSG were made. This lack of data regarding monitoring GH-treated patients with PWS and the inconclusive evidence of the role of GH in the reported sudden death events have led to a therapeutic dilemma for physicians and patients’ families regarding GH therapy and monitoring.

At our institution, patients with PWS who receive GH undergo PSG studies at least yearly or more frequently if snoring worsens to evaluate for sleep-disordered breathing. Those patients who are found to have obstructive apnea events are then evaluated by an otolaryngologist for potential upper-airway surgical intervention. If patients undergo upper-airway surgery, PSG is repeated to evaluate for resolution of apnea events.

There are limited and conflicting data regarding adenotonsillectomy (T&A) in children with PWS, with the largest study consisting of 5 patients. We undertook this retrospective study to evaluate the efficacy of T&A in the treatment of sleep apnea in patients with PWS.

METHODS

A medical chart review was performed at Nationwide Children’s Hospital (NCH) of patients seen at the NCH endocrinology metabolism and diabetes center as well as the Central Ohio Pediatric Endocrinology and Diabetes Services (COPEDS) office in Columbus, Ohio. Subjects were included in the review if they were 19 years or younger, had a diagnosis of PWS confirmed by genetic testing, and underwent T&A, with preoperative and postoperative PSG. Thirteen patients met the criteria for inclusion in this review.

All PSG findings were scored by a board-certified sleep physician (M.S.) according to the pediatric standards for sleep stages and respiratory events defined by the American Academy of Sleep Medicine. The apnea-hypopnea index (AHI) was used to categorize the patient’s sleep-disordered breathing as severe, moderate, or mild. Severe AHI was classified as higher than 10; moderate as higher than 5 to 10; and mild as 1.5 to 5. Patients with obstructive hypoventilation—defined as snoring and partial pressure of carbon dioxide released at end of expiration (end tidal CO2 [ETCO2]) greater than 50 mm Hg for more than 25% of total sleep time—were also included in the mild category, despite having an AHI lower than 1.5.

The study was approved by the Nationwide Children’s Hospital institutional review board. Informed consent and assent were not obtained owing to the retrospective nature of this study.

RESULTS

Of the 13 patients included in the review, 6 were girls (46%); 8 had genetic characteristics consistent with deletion (61%), and the remaining 5 had genetic characteristics consistent with uniparental disomy (39%). The median age at T&A was 3 years (age range, 6 months to 11 years), and the median age at start of GH treatment was 8.5 months (range, 2 months to 6 years) (Table 1).

Nine of the 13 patients had mild to moderate obstructive sleep apnea (OSA) or obstructive hypoventilation (69%); in 8 of these 9, breathing normalized after T&A. Four children had severe OSA prior to surgery (31%), and 2 had normal AHI (<1.5) after surgery (50%) (Table 2) (Figure).

One of the 2 patients whose condition did not improve was an infant who had demonstrated severe OSA at age 6 months (AHI, 12), had undergone T&A at age 7 months, and underwent a subsequent supraglottoplasty at age 14 months for continued OSA. After supraglottoplasty at age 14 months, he had an AHI of 9, with almost equal distribution of central and mixed apneas and hypopneas with snoring during about 50% of sleep time. He was initially treated with a bilevel positive airway pressure (BPAP) device, which was inconsistently worn at home. He was therefore transitioned to supplemental FiO2 (fractional inspired oxygen) therapy at 0.25 L/min via nasal cannula, which was continued for 18 months. He had a normal findings on brain magnetic resonance imaging and mild hypercapnia. His PSG results had normalized by age 35 months, with an AHI less than 1.5 and a maximum ETCO2 of 51 mm Hg breathing room air during sleep. He continued GH treatment throughout and was doing well at last follow-up, age 50 months.

The other child with severe OSA who did not improve after T&A was a 24-month-old girl. She had increased central apnea events and was treated with BPAP with a back-up rate and stabilization. She continued BPAP therapy at last follow-up, age 31 months.

Two children with PWS underwent T&A for obstructive hypoventilation and showed postoperative improvement. One patient was a 6-year-old boy with snoring and an ETCO2 higher than 50 mm Hg for 60% of sleep time prior to surgery. After surgery, the snoring was gone, and
an ETCO2 higher than 50 mm Hg was measured during only 25% of sleep time.

The second child was a 2.5-year-old boy with snoring and an ETCO2 higher than 50 mm Hg during 66% of sleep time. Postoperatively, he had a reduction to only 23% of sleep time with an ETCO2 higher than 50 mm Hg.

Our study showed that T&A is generally effective in most children with PWS who demonstrate mild to moderate OSA but is less likely to be curative in those with severe OSA. Half of the children in the present study with severe OSA prior to surgery continued to have severe sleep-disordered breathing postoperatively. One patient demonstrated increased central apneas on PSG after surgery. We hypothesize that resolution of the OSA component in this patient led to an unmasking of altered control of breathing, with more central apneas and periodic breathing noted.

Our findings are in agreement with Schlueter et al,24 who found continued irregularity in sleep studies after T&A in 3 patients of ages similar to those in our cohort. In addition, they found that hypercapnic ventilator responses in patients with PWS showed lower increments of ventilation than was found among their peers, thus supporting the previous claim of abnormal peripheral chemoreceptor function in PWS.18,24

Our study complements the findings of Pavone et al25 in their review of 5 children with PWS who underwent T&A. In that report, 1 child who initially had moderate OSA normalized after surgery; 3 patients with severe OSA and 1 patient with moderate OSA by AHI score improved to mild OSA. Although their study showed improvement in all AHI scores after T&A in the PWS population they reviewed, the patients did not completely normalize. This is concordant with our finding that 38% of the patients with PWS continued to have at least mild OSA after T&A.

Our study also adds useful information about a younger age group. Pavone et al25 studied children with a me-

Table 1. Baseline Characteristics of the 13 Patients Included in the Review

<table>
<thead>
<tr>
<th>Patient No./Sex/Age at T&amp;A, y</th>
<th>Genetics</th>
<th>Age at GH Start</th>
<th>Weight, kg</th>
<th>Preoperative BMI</th>
<th>BMI z score</th>
</tr>
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<tbody>
<tr>
<td>1/F/11.00</td>
<td>Deletion</td>
<td>Unknown</td>
<td>76.2</td>
<td>29.1</td>
<td>2.28</td>
</tr>
<tr>
<td>2/F/1.75</td>
<td>Deletion</td>
<td>4 mo</td>
<td>9.6</td>
<td>15.1</td>
<td>-0.90</td>
</tr>
<tr>
<td>3/M/2.25</td>
<td>UPD</td>
<td>9 mo</td>
<td>13.4</td>
<td>16.4</td>
<td>-0.10</td>
</tr>
<tr>
<td>4/F/3.5.0</td>
<td>Deletion</td>
<td>6 mo</td>
<td>17.1</td>
<td>21.1</td>
<td>2.73</td>
</tr>
<tr>
<td>5/M/2.75</td>
<td>UPD</td>
<td>5 mo</td>
<td>18.8</td>
<td>20.8</td>
<td>2.86</td>
</tr>
<tr>
<td>6/M/2.60</td>
<td>Deletion</td>
<td>5 mo</td>
<td>18.0</td>
<td>21.2</td>
<td>3.91</td>
</tr>
<tr>
<td>7/F/4.00</td>
<td>UPD</td>
<td>8 mo</td>
<td>16.0</td>
<td>17.7</td>
<td>3.84</td>
</tr>
<tr>
<td>8/F/3.00</td>
<td>UPD</td>
<td>14 mo</td>
<td>15.9</td>
<td>5.6</td>
<td>1.52</td>
</tr>
<tr>
<td>9/M/2.75</td>
<td>Deletion</td>
<td>&lt;1 y</td>
<td>19.6</td>
<td>19.7</td>
<td>-1.51</td>
</tr>
<tr>
<td>10/M/5.50</td>
<td>Deletion</td>
<td>18 mo</td>
<td>27.0</td>
<td>4.0</td>
<td>3.10</td>
</tr>
<tr>
<td>11/M/6.00</td>
<td>Deletion</td>
<td>6 y</td>
<td>23.1</td>
<td>21.2</td>
<td>2.35</td>
</tr>
<tr>
<td>12/M/0.50</td>
<td>Deletion</td>
<td>2 mo</td>
<td>7.9</td>
<td>16.1</td>
<td>NR</td>
</tr>
<tr>
<td>13/F/9.40</td>
<td>UPD</td>
<td>3 y</td>
<td>55.2</td>
<td>29.1</td>
<td>2.18</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GH, growth hormone therapy; NR, not reported; T&A, adenotonsillectomy; UPD, uniparental disomy.

Table 2. Patient-Specific Data on Preoperative and Postoperative AHI

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Preoperative AHI</th>
<th>Postoperative AHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.0 (Moderate)</td>
<td>3.0 (Mild)</td>
</tr>
<tr>
<td>2</td>
<td>21.8 (Severe)</td>
<td>24.4 (Severe)</td>
</tr>
<tr>
<td>3</td>
<td>3.0 (Mild)</td>
<td>0.5 (Normal)</td>
</tr>
<tr>
<td>4</td>
<td>0.2 (Normal)</td>
<td>0.2 (Normal)</td>
</tr>
<tr>
<td>5</td>
<td>13.0 (Severe)</td>
<td>1.2 (Normal)</td>
</tr>
<tr>
<td>6</td>
<td>8.0 (Moderate)</td>
<td>2.0 (Mild)</td>
</tr>
<tr>
<td>7</td>
<td>13.9 (Severe)</td>
<td>0.1 (Normal)</td>
</tr>
<tr>
<td>8</td>
<td>2.0 (Mild)</td>
<td>0.0 (Normal)</td>
</tr>
<tr>
<td>9</td>
<td>1.4 (Normal)</td>
<td>0.9 (Normal)</td>
</tr>
<tr>
<td>10</td>
<td>5.0 (Mild)</td>
<td>2.4 (Mild)</td>
</tr>
<tr>
<td>11</td>
<td>0.3 (Normal)</td>
<td>0.0 (Normal)</td>
</tr>
<tr>
<td>12</td>
<td>12.0 (Severe)</td>
<td>26 (Severe)</td>
</tr>
<tr>
<td>13</td>
<td>6.0 (Moderate)</td>
<td>1.0 (Normal)</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GH, growth hormone therapy.

Figure. Preoperative and postoperative apnea hypopnea index (AHI) in children with Prader-Willi syndrome.

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dian age of 4.5 years (youngest age, 1.9 years). The patients in our study had a median age of 3 years, and the youngest patient was only 6 months old. The younger age in our cohort may have affected our results from T&A. The 2 children with the highest postoperative AHI at ages 4 months and 2 months, respectively. Starting GH therapy at a younger age may have contributed to their development of OSA at a younger age, since GH has been known to cause tonsillar and adenoid hypertrophy.20 Starting GH therapy before age 4 months has now become common practice, and this makes our results more pertinent, as we encounter sleep-disordered breathing at younger ages than previously reported.

Our retrospective study is limited by potential selection bias. It has now become our practice to conduct PSG testing yearly on all infants and children with PWS who receive GH therapy. This leads to an underrepresentation of patients with PWS who are not receiving GH therapy, and therefore, no conclusions can be drawn from our data about the role of GH in the development of sleep-disordered breathing. In addition, since sleep studies are being conducted more often than annually in infants and children with symptoms like snoring, we risk selection bias for patients with more severe disease. A prospective study to further evaluate the issue of apnea and the role of PSG in the prevention of sudden death is neither practical nor ethical. So this retrospective study does provide useful information.

Currently, recommendations for PSG in children with PWS are at initiation of GH therapy and then if symptoms of snoring and daytime sleepiness worsen.21 We have found that patients with PWS can have continued sleep-disordered breathing after T&A due to either residual obstructive apnea with snoring or altered respiratory control with more central apneas and periodic breathing. Central apneas including periodic breathing may be quieter at night and go unnoticed using the current guidelines of increased snoring for PSG evaluation.

Our results are consistent with those of a larger study of children with OSA but without PWS, which showed that 30% to 40% of obese children did not normalize their AHI after T&A regardless of the degree of preoperative severity.23 This underscores the contribution of both body habitus and lymphoid tissue hypertrophy to OSA.

We conclude that although T&A does improve sleep apnea in all children, especially those with severe OSA. The ability to monitor and treat these children depends on close collaboration between endocrinologists, otolaryngologists, and sleep medicine specialists to optimize outcome in these children. Yearly PSGs and careful study postoperatively and after changes in breathing patterns, including development of apneic pauses without snoring, appear to be critical, especially in younger patients with PWS receiving GH therapy.

Submitted for Publication: May 14, 2012; final revision received July 2, 2012; accepted July 16, 2012.

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Author Contributions: Dr Meyer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Meyer, Splaingard, Repaske, Atkins, and Jatana. Acquisition of data: Meyer, Splaingard, Zipf, and Jatana. Analysis and interpretation of data: Meyer, Repaske, Zipf, and Jatana. Drafting of the manuscript: Meyer, Splaingard, Zipf, and Jatana. Critical revision of the manuscript for important intellectual content: Meyer, Splaingard, Repaske, Zipf, Atkins, and Jatana. Statistical analysis: Meyer. Administrative, technical, and material support: Splaingard, Repaske, and Jatana. Study supervision: Splaingard, Repaske, Zipf, and Jatana.

Conflict of Interest Disclosures: None reported.

Previous Presentations: This article was presented at the National Prader-Willi Association Meeting; November 11, 2011; Orlando, Florida; and at the Pediatric Academic Society Meeting; April 28, 2012; Boston, Massachusetts.

REFERENCES


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