

## Prader Willi Syndrome and Obstructive Sleep Apnea: Co-occurrence in the Pediatric Population

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**Background:** A high prevalence of obstructive sleep apnea (OSA) occurs in children with Prader-Willi syndrome (PWS). Yet, due in part to the relatively small samples previously used, the prevalence of OSA has varied greatly across studies. It is also unclear if factors such as age, gender, body mass index (BMI), or type of genetic imprinting are associated with increased risk for OSA among children with PWS.

**Objectives:** To evaluate the (a) prevalence of OSA, as well as narcolepsy, in pediatric populations diagnosed with PWS; (b) effects of age, gender, body mass index, and genetic imprinting on OSA severity; and (c) efficacy of adenotonsillectomy (AT) for decreasing OSA severity in this population.

**Methods:** All studies assessing OSA among children with PWS through August 2013 were identified using the PubMed/Medline, Psych Info, Cochrane library, and Google Scholar data bases.

**Results:** Fourteen studies of children diagnosed with PWS and who were assessed for OSA using polysomnography (PSG) met inclusion criteria (n = 224 children). The prevalence

of OSA across studies was 79.91% (n = 179/224). Among youths with OSA, 53.07% had mild OSA, 22.35% moderate OSA, and 24.58% severe OSA. Narcolepsy was found to occur in 35.71% of children with PWS. Adenotonsillectomy was associated with improvement in OSA for most children with PWS. However, residual OSA was present in the majority of cases post-surgery.

**Conclusion:** This study confirms the high prevalence of OSA and narcolepsy among children with PWS. Screening for OSA and narcolepsy among children with PWS is recommended. In addition, while adenotonsillectomy was effective in reducing OSA for some children, alternative treatments may need to be considered, given the only moderate response rate.

**Keywords:** Prader-Willi syndrome, sleep disordered breathing, obstructive sleep apnea, narcolepsy, meta-analysis

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Prader-Willi syndrome (PWS) is a genetic disorder affecting chromosome 15q11-q13. It has a prevalence of 1:10,000-25,000 live children and occurs secondary to paternal chromosomal deletion in 70% to 75% of cases, or with maternal disomy occurring in 20% to 25% of cases.<sup>1</sup> In addition, there is abnormal methylation of chromosome 15 in 2% to 5% of cases.<sup>2</sup> Children presenting with this disorder are characterized by severe hypotonia and feeding difficulties leading to failure to thrive in infancy. By the second year of life, however, excessive eating secondary to hypothalamic dysfunction can lead to morbid obesity. Other associated symptoms include delays in motor and language development, and low intelligence. Hypogonadism in both males and females, short stature, scoliosis, and strabismus are also associated symptoms.<sup>3</sup> It is important to note that hypothyroidism, a comorbid disorder sometimes present in children with PWS, has been associated with obstructive sleep apnea (OSA).<sup>2</sup>

Angelman syndrome (AS) is very closely associated with PWS, as both syndromes are characterized by deficiency in expression of the long arm of chromosome 15.<sup>4</sup> However, in PWS, the genes are deleted or unexpressed on paternal chromosomes, whereas the maternal gene is deleted or inactive in AS. Behavioral and endocrinal abnormalities (e.g., irritability with outbursts and hypothalamic insufficiency) are more severe in PWS patients, possibly suggesting a higher incidence of

### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Prevalence rates of OSA are high among children with PWS, but vary greatly across studies. It is unknown if factors such as age, gender, body mass index, or type of genetic imprinting are related to OSA risk among children with PWS. It is not clear if AT has the same curative effects in children with PWS as compared to the general population. Thus, this study assessed changes in the prevalence of OSA following AT. Controversies about the prevalence of narcolepsy also exist in this population.

**Study Impact:** Since there is a high prevalence of OSA among PWS patients, routine screening for OSA by PSG is essential for early detection and treatment of this disorder. Although AT is often a curative treatment for children with OSA, it might not be as effective for children with PWS. Thus, post-AT PSG is essential to assess the OSA severity and to consider additional treatment if required. Screening for narcolepsy in this population is also essential after resolution of OSA since there is a high prevalence.

narcolepsy in this population. In AS, cognitive and neurological consequences (e.g., severe mental retardation, ataxia, and seizures) are more pronounced and severe.<sup>4</sup> AS is believed to occur at about the same prevalence as PWS; however, in contrast to PWS which has three distinct types, AS has four: deletions, paternal disomy, methylation mutation, and single gene mutation (UBE3A).<sup>5</sup> In AS, OSA occurs at a higher rate than in the general population, but probably with lower prevalence than

among PWS patients. In a study involving ten children with AS, 30% were found to have OSA, diagnosed by an AHI cutoff of 5 per hour.<sup>15</sup>

OSA occurs in 2% to 3% of children and/or adolescents in general community samples.<sup>6</sup> In contrast, rates of OSA among children with PWS range from 44% to 100%.<sup>7-13</sup> The increase in viscosity of secretions, craniofacial abnormalities causing small airways, and hypotonia leading to airway collapsibility all contribute to the higher prevalence of OSA in this population. Secondary alveolar hypoventilation can also occur among children with PWS. Thus, baseline polysomnography (PSG) has been recommended in this population as infants and in early childhood to screen for any breathing problems.<sup>14</sup> Aside from high rates of OSA, children with PWS also have a higher prevalence of short sleep onset latency and REM latency, and sleep onset REM (SOREM) due to central hypothalamic dysfunction.<sup>2</sup> Thus, a higher prevalence of narcolepsy also has been suggested among youths with PWS.<sup>2</sup>

Although the prevalence of OSA in PWS patients is known to be high, it varies considerably across studies. Accordingly, one purpose of the current study was to examine several potential moderators of OSA prevalence among children with PWS, including child age. Some studies have found a higher incidence of OSA in the first two years of life.<sup>14</sup> This might be secondary to the presence of central apnea that occurs more often at this age. However, there is also reason to believe that children with PWS might be less likely to have OSA during infancy because their overeating and obesity, a risk factor for OSA, does not tend to occur until after the first two years of life.<sup>16</sup> Thus, it remains unclear whether the prevalence of OSA varies with age.

Gender is a second potential moderator of OSA prevalence. Gender differences are found among adults with OSA in community samples without PWS, as men exhibit higher rates of OSA,<sup>17</sup> although most studies of children suggest an equal prevalence of OSA in gender.<sup>18</sup> With puberty, a gradual increase in prevalence occurs in males due to hormonal changes and/or possessing a longer upper airway leading to higher risk of airway collapse during sleep.<sup>18</sup> An increase in OSA occurs in post-menopausal women, suggesting a hormonal protective role.<sup>19</sup> However, patients with PWS have associated hypogonadism; thus, it is expected that gender differences would not be seen following puberty, due to the lack of hormonal production in females. A third potential moderator is BMI, as obesity, a common sign among children with PWS, has been related to worsening OSA in children without a genetic abnormality.<sup>20</sup> However, it remains unclear as to whether this plays a significant factor in increasing risk of OSA among children with PWS. Finally, genetic imprinting has not been examined for its potential effect on OSA in prior research of children with PWS. Thus, age, gender, BMI, and genetic imprinting were examined as potential moderators of differences in prevalence rates of OSA among children with PWS.

Untreated OSA in children has been associated with a diversity of health problems. Lower cognitive function has been detected in children with untreated OSA compared to controls in non-genetically abnormal children.<sup>21</sup> Later in life, OSA is associated with cardiovascular complications including high blood pressure, heart disease, and even strokes.<sup>22,23</sup> Attention

problems, hyperactivity and other psychiatric problems such as increased depressive symptoms are also more common among children with OSA.<sup>24-26</sup> Thus, effective treatment of OSA may prevent negative long-term consequences. Adenotonsillectomy (AT) has been the main treatment in non-genetically impaired children with OSA, and has been found to cure OSA in up to 60% to 85% of children with OSA.<sup>27</sup> Other treatments for OSA can include use of a dental device or continuous pressure ventilation, and in rare cases, tracheotomy. The effectiveness of AT in treating OSA among children with PWS is largely unknown, as AT treatment studies have generally excluded patients with genetic abnormalities or those with facial dysmorphism. In children with PWS, however, the causes of upper airway narrowing include hypotonia affecting upper airway muscles, facial dysmorphism and mid facial hypoplasia, restriction in lung volume secondary to obesity and scoliosis, and the hypothalamic abnormalities leading to central apneas. Thus, AT would be expected to help but not necessarily cure the OSA. We analyzed the limited published data on the effectiveness of AT to treat OSA among children with PWS.

The goals of the current quantitative review are to (a) examine the overall prevalence of OSA and narcolepsy among children with PSW given the variable prevalence rates across studies; (b) explore whether OSA appears to vary as a function of age, gender, BMI, and genotype among children with PSW; and (c) examine the efficacy of adenotonsillectomy in treating OSA in children with PSW.

## METHODS

### Study Selection

The PubMed/Medline, PsychInfo, Cochrane library, and Google Scholar data bases were searched using the terms “Prader Willi syndrome” crossed by “sleep disordered breathing,” “SDB,” “obstructive sleep apnea,” or “OSA” and further crossed by “child,” “children,” or “adolescents.” English-language studies through August 2013 were examined.

### Inclusion and Exclusion Criteria

Published studies including children less than 18 years of age diagnosed with PWS were included. However, a small number of studies included adult subjects and were included for comparison purposes. Selection and coding of information was conducted by the first author and included sample size, age, gender, BMI, and apnea-hypopnea index (AHI) or respiratory measure.

To assess the incidence and severity of OSA, only studies including PSG were included since it is the gold standard diagnostic test.<sup>28</sup> Seventeen published studies were initially identified.<sup>1,7-14,29-36</sup> Four studies did not report the use of individual AHI scores for patients.<sup>1,10,29,31</sup> Attempts were made to contact authors to obtain individual level data, which one author provided<sup>10</sup>; the other 3 studies were excluded from the review. An additional study was partially included, but only to assess the prevalence of OSA in patients with PWS<sup>11</sup> as it did not report individual AHI scores but did reports the percentage of OSA in their population. Thus, 14 studies satisfied the inclusion criteria (**Table 1**).<sup>7-11,12-14,30,32-36</sup> To minimize publication bias,

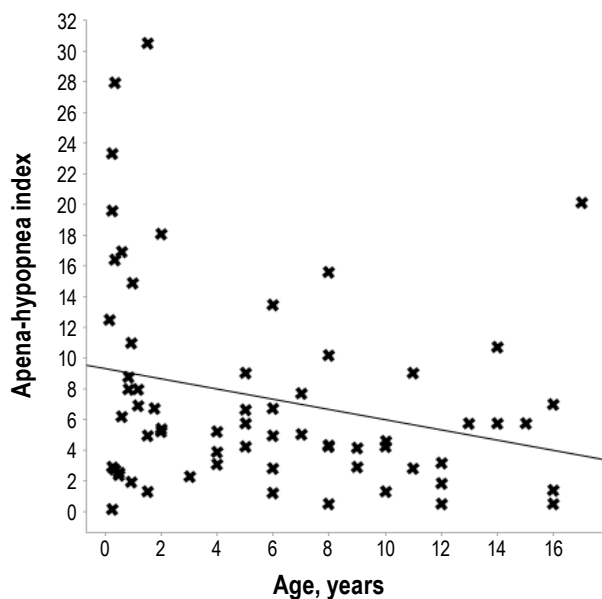
**Table 1**—Demographics and characterization of children included in this analysis

Author, Year	Mean Age (SD)	Number of Children (% Male)	History of AT	History of GH	Categories of OSA	Percent of OSA	Referral Source
Al-Saleh S et al., 2013	0.8-15.4 (5.36 ± 4.66)	15 (73.33%)	Unknown AT	No GH	Mild = 90.91%; Moderate = 9.09%; Severe = 0	73.33% (AHI = 2.7 ± 2.04)	Children undergoing GH treatment. Exclusion of severe OSA.
Lin H-Y et al., 2007	1.2-15.6 (5.83 ± 3.76)	29 (51.72%)	No AT	No GH	Mild = 51.72%; Moderate = 31.03%; Severe = 17.24%	100% (AHI = 5.83 ± 3.76)	Random PWS cases.
Williams K et al., 2007	1.2-17.8 (7.96 ± 4.61)	34 (57%)	Unknown	Some received GH	Mild = 46.67; Moderate = 3.33; Severe = 50.0%	88.24% (AHI = 19.30 ± 27.72)	Sleep center having PWS children suspected of OSA.
Miller J et al., 2006	0.17-1.75 (0.67 ± 0.45)	20 (60%)	No AT	No GH	Mild = 36.84%; Moderate = 26.32%; Severe = 36.84%	95.0% (AHI = 9.30 ± 7.87)	PWS patients undergoing GH treatment.
O'Donoghue FJ et al., 2005	1.5-17.0 (6.71 ± 5.87)	7 (28.57%)	Unknown	Unknown	Mild = 42.86%; Moderate = 14.29%; Severe = 42.86%	100% (AHI = 13.06 ± 10.10)	Random PWS cases.
Manni R et al., 2001	8.0-16.0 (13.13 ± 2.90)	8 (12.5%)	Unknown	Unknown	Mild = 40%; Moderate = 60%; Severe = 0	62.50% (AHI = 3.3 ± 3.41)	Random PWS cases from pediatrics and sleep center.
DeCock V et al., 2011	8-21	8 (37.5%)	Unknown	Unknown		25%	PWS children with excessive daytime sleepiness.
Vandeleur M et al., 2013	0-18	34	Unknown	No GH	Mild = 80%; Moderate = 6.67%; Severe = 13.33%	44%	Retrospective study on children undergoing GH treatment.
Zanella S et al., 2009	0.17-0.5	3	Unknown	Unknown	Mild = 66.67%	66.67%	3 random PWS children cases.
Harris JC et al., 1996	5.5-21	5 (40%)	Unknown	Unknown			Random 8 PWS patients.
Vandenbushe NL et al., 2007	5.67 (0-15)	3 (66.67%)	Unknown	Unknown	Mild = 33.34%; Severe = 33.34%	66.67%	5 cases with PWS who also had sleep problems.
Nevismalova et al., 2005	3.1 (one child)	One male	Unknown	Unknown			Random 4 PWS patients studied for narcolepsy diagnosis.
Hiroe Y et al., 2000	4 (1.2-6.8)	2 (50%)	Unknown	Unknown	Mild = 50%; Moderate = 50%	100%	3 children with PWS who presented with EDS.
Feston DA et al., 2006	unknown	54	Unknown	Unknown	Mild = 43.39%; Moderate = 30.19%; Severe = 18.86%	92.45%	Randomized prospective trials for PWS undergoing GH treatment.

we searched for unpublished data, including dissertations. No unpublished dissertations were found to have PSG screening in the PWS population. When examining potential moderators, all studies included the age of each participant, but only 9 studies included the gender of each participant. Across studies, we divided participant age into the following 4 groups: age 2 years or younger since some studies suggest a higher prevalence of OSA in this age group<sup>14</sup>; 2.1 to 7.0 years (since this is the age when adenoidal and tonsillar enlargement occur most frequently); 7.1 to 14.0 years of age; and a final group from 14.1 to 18 years old.

Of note, 4 of the included studies focused on children with PWS undergoing growth hormone treatment who were recruited from pediatric clinics,<sup>9,11,13,30</sup> and 2 others consisted

of children with PWS who were randomly chosen from pediatric clinics.<sup>7,8</sup> Four other studies consisted of children with PWS who presented to sleep clinics with sleep disorders,<sup>12,32,35,36</sup> possibly inflating the prevalence of OSA, while 2 others included children who were randomly selected from the community and referred to the sleep clinic.<sup>10,33</sup> The remaining 2 studies consisted of children with PWS who were selected from a sleep laboratory referral and thus also might have inflated the prevalence of OSA.<sup>14,34</sup> We further analyzed the prevalence of OSA in the following 4 groups to see if referral source was associated with OSA prevalence: those randomly selected from pediatric clinic<sup>7,8</sup> (2 studies), those referred from pediatric clinic undergoing growth hormone administration<sup>9,11,13,30</sup> (4 studies), those randomly selected from a sleep center<sup>10,33</sup> (2 studies),

**Figure 1**—Scatterplot of the relation between apnea-hypopnea index and age

and lastly those referred to a sleep center with possible OSA or excessive daytime sleepiness suggesting narcolepsy<sup>12,32,35,36</sup> (4 studies).

Narcolepsy is subdivided into cases with cataplexy (cataplexy by itself is sufficient to diagnose the disorder), without cataplexy (daytime sleepiness in addition to  $\geq 2$  sleep onset REM periods in 4 or 5 naps on the mean sleep latency test [MSLT]), and those secondary to a medical condition. Since most of the studies included in our analysis did not screen for other narcolepsy symptoms, diagnoses depended mainly on the presence of  $\geq 2$  sleep onset REM periods. To assess the incidence of narcolepsy in this population, studies were screened for children with PWS who were assessed using the mean sleep latency test. There was one study that documented cataplexy symptoms, and children were included even if their MSLT was negative.

## RESULTS

### Prevalence of OSA

Among the 14 included studies of 224 children and/or adolescents diagnosed with PWS, the prevalence of OSA was 79.91% (179/224; **Table 1**). Mild sleep apnea (apnea-hypopnea index [AHI] between 1 and 5/h) was diagnosed in 53.07% of cases, moderate sleep apnea (AHI 5-10/h) in 22.35%, and severe cases (AHI  $> 10$ /h) in 24.58%.

To test whether the site of referral was associated with differences in the prevalence of OSA, we divided studies into the following 4 referral groups: children referred from pediatric clinics who were randomly chosen showed an OSA prevalence of 91.89% (34/37), while those from pediatric clinics who were undergoing growth hormone treatment had a prevalence of 77.05% (94/122). Children with PWS referred to sleep clinics who were randomly chosen had a prevalence of 91.67%

(11/12), while those referred to a sleep clinic due to suspected OSA or narcolepsy actually had a relatively low prevalence rate of 73.91% (34/46). However, there was one study assessing narcolepsy that biased this last group in that they had a high number of children with PWS who did not have OSA (87.5% did not have OSA).<sup>35</sup> When excluding this study, the prevalence of OSA in this population was 86.84%. Examining the 4 original groups, referral source was not significantly related to OSA prevalence ( $\chi^2(3) = 5.95$ ,  $p = 0.11$ )

### Gender

Among the 9 studies that included gender ( $n = 87$  children), 85.06% were diagnosed with OSA as detected by PSG (74/87). Of the 74 positive cases, 43 were male and 31 female, with all 4 negative cases being female ( $\chi^2(1) = 3.10$ ,  $p = 0.08$ ). Examining severity of OSA, mild OSA was diagnosed in 33.78% of boys ( $n = 25$ ) vs. 16.22% of girls ( $n = 12$ ), moderate OSA in 12.16% of boys (9) vs. 16.22% of girls (12), and severe OSA in 12.16% of boys (9) vs. 9.46% of girls (7).

### Age

When analyzing the 4 age groups across the 12 studies that provided individual age data (after excluding two studies that only had the average age<sup>11,30</sup>), 88.89% (32/36) of children aged 2 or younger had OSA. This is compared to 88.89% (32/36) in the  $> 2$  to  $\leq 7$ -year age group, 86.49% (32/37) in the  $> 7$  to  $\leq 14$ -year age group, and 76.19% (16/21) in the  $> 14$  to  $\leq 18$ -year age group. Thus, age did not affect the prevalence of OSA among children with PWS ( $\chi^2(3) = 2.20$ ,  $p = 0.53$ ). In addition, 25 adults (age 19 to 46 years) with PWS from 9 studies were compared to the children with PWS. A lower prevalence of OSA was observed among the adults (60.0%; 15/25) than children ( $\chi^2(1) = 5.18$ ,  $p = 0.02$ ). Examining OSA severity as assessed by AHI scores (mild, moderate and severe) as a function of children's age indicated greater severity with younger age ( $r = -0.34$ ,  $p = 0.0018$ ; see **Figure 1**). This finding of decreasing prevalence with age is suggestive of possible improvement over time among both males ( $n = 39$  children,  $r = -0.34$ ,  $p = 0.03$ ) and females ( $n = 45$ ,  $r = -0.32$ ,  $p = 0.03$ ).

### Type of Chromosome Abnormality

Six studies included genetic chromosomal abnormality information for children ( $n = 102$ ). Deletion of parental chromosome abnormality was present in 66.67% of the population (68/102), with maternal disomy diagnosed in 28.43% (29/102) and imprinting center mutation in 4.90% (5/102). Rates of OSA were highly similar between the deletion of parental chromosome abnormality and maternal disomy groups ( $\chi^2(1) = 0.08$ ,  $p = 0.77$ ). Examining OSA severity levels in parental chromosome abnormality children compared to maternal disomy, 14.71% vs. 17.24% in the respective groups had no OSA; 41.18% vs. 37.93% had mild OSA; 17.65% vs. 17.24% had moderate OSA; and 26.47% vs. 27.59% had severe OSA, respectively. The rate of OSA among the imprinting center mutation group was 80% (4/5).

### BMI

Z-scores for BMI, which were normed for age and gender, were assessed in 3 studies involving 47 children. OSA

did increase with greater BMI ( $r = 0.34$ ,  $p = 0.018$ ). BMI percentage, again normed for age and gender, was assessed in 19 children across 3 studies. As was the case for BMI z-scores, OSA was also associated with greater BMI percentiles ( $r = 0.49$ ,  $p = 0.035$ ).

### Narcolepsy

Six studies assessed children with PWS ( $n = 42$ ) using MSLT and/or screening for cataplexy symptoms. The prevalence of signs/symptoms suggestive of narcolepsy was 35.71% (15/42).

### Adenotonsillectomy as a Treatment for OSA

Since adenotonsillectomy is generally the treatment of choice for children with OSA, the effect of AT was assessed in children with PWS. Pre-surgery data including children with PWS undergoing AT to treat their OSA was compared with post-AT AHI levels. Four studies were included in the analysis totaling 17 children with OSA, whose follow-up period ranged from 3 to 43 months post-AT surgery. There were 4 studies included in this analysis.<sup>37-40</sup> Seven children had a normal AHI level after AT (41.18%; 2 were normal at baseline). Six children had mild OSA (35.29%), one had moderate OSA (5.88%), and 3 had severe OSA (17.65%) following surgery. It is important to note that 2 cases had worsening of their OSA (one of each gender), while one had the same severity level of AHI (female).

## DISCUSSION AND CONCLUSION

Obstructive sleep apnea prevalence rates range between 44% and 100% in the published reports. Our quantitative review suggests an overall prevalence rate of 79.91%, equally distributed between the two genders. This rate is substantially higher than the typical prevalence of OSA among community samples of children, which range around 2% to 3%.<sup>6</sup> Several risk factors may help to explain this relationship, however, including obesity leading to fatty deposition around the neck and subsequent airway narrowing. Both obesity and scoliosis can limit lung capacity as well.<sup>3</sup> Reduced respiratory response to hypoxia and hypercapnia are prevalent in this population, independent of obesity risk.<sup>41</sup> Fifty-three percent of children with PWS had mild forms of OSA, while 22% and 25% were for moderate or severe OSA, respectively. The Clinical Advisory Board of the PWS Association recommends a PSG study in all PWS children with interpretation by a sleep specialist.<sup>42</sup> They also recommend expediting the PSG in cases of severe obesity, chronic respiratory infection, asthma, snoring or witnessed apnea, or EDS before AT or other surgeries that require sedation and prior to initiating GH.

Our study has found comparable rates across all age groups (86% to 89% for 3 age groups < 14 years of age). Although it is expected that adenotonsillar enlargement occurs in the 2- to 7-year age group, this group did not show a higher prevalence of OSA compared to those older or younger. However, when using AHI severity as the measure of OSA, a significant correlation was found, such that younger age was associated with higher AHI scores for both genders.

Analyses of the published data on adult individuals with PWS have yielded a much lower incidence of OSA (60% vs. the 80% we found for children). This might be explained by

either the presence of a wider airway present among adults or that some adults had AT which in turn improved their OSA. However, grading difference in OSA in adults compared to children also might have played a role, as there is a 5 apnea/hypopnea per hour grading difference when assessing OSA in children vs. adults. Another methodological difference is that OSA is considered present for children following two or more missed breaths, whereas OSA is considered present for adults when the respiratory event lasts at least ten seconds.<sup>43</sup> Thus, scoring differences can lead to the detection of more OSA events in children compared to adults.

Children suffering from OSA have been found to have increased rates of behavioral problems (e.g., inattention, hyperactivity, and irritability).<sup>24,26</sup> These studies have excluded children with severe neurological or genetic disorders. Controversy exists, however, as to whether specific genetic subtypes are related to behavioral and psychiatric problems among children with PWS.<sup>44</sup> Some authors suggest worse behavioral problems and greater comorbidity with the maternal disomy, while others suggest higher severity in the paternal deletion type.<sup>44</sup> Examining OSA rather than behavioral problems, our analysis did not yield a relationship between the genetic type and OSA.

Since AT was the treatment of choice for children with OSA, we examined its efficacy in improving OSA among patients with PWS. Several studies have found either partial or a complete lack of response to AT.<sup>1,37-39</sup> In addition, one study suggests weight gain after AT, a major correlate to worsening of OSA.<sup>45</sup> In our review, 46.67% of children with PWS had normal AHI after the surgery (including two children who had normal AHI scores before surgery). The literature suggests that 60% to 85% of children without facial dysmorphism or genetic abnormalities who have OSA have normal AHI after AT.<sup>46,47</sup> Thus, this study highlights that while many children with PWS exhibit improved OSA following AT and that their response rate is substantial, it is still less than that of children without PWS. Our findings confirm the need to screen children with PWS after surgery for OSA (even in asymptomatic cases). There are several studies suggesting the effectiveness of intranasal steroids and leukotriene antagonists to be effective in treating OSA cases.<sup>47</sup> Antibiotics can treat any associated adenotonsillar infections but usually do not lead to cure of OSA. In moderate to severe residual OSA, continuous pressure ventilation is an appropriate option. Compliance with this latter treatment is improved when combined with behavioral interventions. Dental devices have also been used; however, compliance issues and lack of research on their long-term effects limit their use.<sup>47</sup> Adenoidal enlargement also can reoccur, requiring further surgeries. Supplemental oxygen has sometimes been used in individuals presenting with frequent oxygen desaturations. Weight loss can lead to improvement of OSA in some patients. However, since there are other etiologies causing OSA (e.g., hypotonia), it is rarely the cure. In the obese adolescent population, bariatric surgery has shown improvements in OSA.<sup>48</sup> However, this treatment modality is usually reserved for those who are morbidly obese and have failed dietary adjustment. Other surgery alternatives include nasal reconstruction (for septal deviation or turbinate enlargement), rapid maxillary expansion, and mandibular advancement surgeries<sup>49</sup>; however, these treatment options are not well studied in children.

Tracheostomy, while previously used to treat severe cases, is rarely used due to its complications.<sup>50</sup>

Narcolepsy is a neurological disorder characterized by cataplexy, excessive daytime sleepiness, hypnagogic and hypnopompic hallucinations, and sleep paralysis. Although it is a clinical diagnosis, MSLT is used to confirm the diagnosis in atypical cases. A high prevalence of narcolepsy has been previously suggested among children with PWS, partly due to the hypothalamic abnormalities associated with the syndrome. In our analysis, 35.71% of individuals had two or more SOREMs. However, a positive MSLT might have been secondary to OSA leading to interrupted sleep and delayed REM periods. There is also a population that would be categorized as having narcolepsy with cataplexy based on the presence of cataplexy alone; this was not screened for in most of the included studies.

Several factors might have affected the results of this study. There are limited published studies involving PWS, partly due to its low prevalence. Even in the published cases, the number of included individuals was often modest; thus, many studies used the median AHI score for analysis. Second, it is possible that referral source could have affected OSA prevalence rates across studies. However, examining prevalence rates by referral source (e.g., whether from a pediatric clinic versus a sleep clinic), we did not find evidence of differences due to referral source. Third, there is the possibility of selection bias, even in the randomized studies. We tried to minimize this by including any unpublished data. However, we could not find any unpublished data that met our inclusion criteria.

The current review highlights the high prevalence of OSA in children with PWS compared to general community samples of children. Since untreated OSA can lead to a diversity of medical, cognitive, and/or psychiatric complications, routine screening of this population is essential. PSG is the gold standard screening tool, especially given the lack of reliable correlations between symptomatic complaints and the presence of OSA. Since AT can improve, but does not usually cure the OSA of children with PWS, post-AT PSG is essential, especially in those with severe OSA. Other treatment methods should be considered if necessary (e.g., continuous pressure ventilation, or dental device) in children with residual OSA. Due to the high rate of narcolepsy prevalent in this population, causes of excessive daytime sleepiness also should be ruled out. Stimulant medications (e.g., modafinil, methylphenidate or mixed amphetamine salts) have been indicated to improve excessive daytime sleepiness in individuals with narcolepsy.<sup>51</sup>

## REFERENCES

1. DeMarcantonio MA, Darrow DH, Gyurisko E, Derkay CS. Obstructive sleep disorders in Prader-Willi syndrome: The role of surgery and growth hormone. *Int J Pediatr Otorhinolaryngol* 2010;74:1270-2.
2. Nixon GM, Brouillette RT. Sleep and breathing in Prader-Willi syndrome. *Pediatr Pulmonol* 2002;34:209-17.
3. Holm VA, Cassidy SB, Butler MG, Hanchett JM, et al. Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics* 1993;91:398-402.
4. Cassidy SB, Dykens E, Williams CA. Prader-Willi and Angelman syndromes: Sister imprinted disorders. *Am J Med Genet* 2000;97:136-46.
5. Engels JV. *Focus on birth defects research*: Nova Publishers; 2006.
6. Brunetti L, Rana S, Lospalluti ML, et al. Prevalence of obstructive sleep apnea syndrome in a cohort of 1,207 children of southern Italy. *Chest* 2001;120:1930-5.
7. Lin HY, Lin SP, Lin CC, et al. Polysomnographic characteristics in patients with Prader-Willi syndrome. *Pediatr Pulmonol* 2007;42:881-7.

8. Manni R, Politini L, Nobili L, et al. Hypersomnia in the Prader Willi syndrome: clinical-electrophysiological features and underlying factors. *Clin Neurophysiol* 2001;112:800-5.
9. Miller J, Silverstein J, Shuster J, Driscoll DJ, Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab* 2006;91:413-7.
10. O'Donoghue FJ, Camfferman D, Kennedy JD, et al. Sleep-disordered breathing in Prader-Willi syndrome and its association with neurobehavioral abnormalities. *J Pediatr* 2005;147:823-9.
11. Vandeleur M, Davey MJ, Nixon GM. Are sleep studies helpful in children with Prader-Willi syndrome prior to commencement of growth hormone therapy? *J Paediatr Child Health* 2013;49:238-41.
12. Williams K, Scheimann A, Sutton V, Hayslett E, Glaze DG. Sleepiness and sleep disordered breathing in Prader-Willi syndrome: relationship to genotype, growth hormone therapy, and body composition. *J Clin Sleep Med* 2008;4:111-8.
13. Al-Saleh S, Al-Naimi A, Hamilton J, Zweerink A, Iaboni A, Narang I. Longitudinal evaluation of sleep-disordered breathing in children with Prader-Willi Syndrome during 2 years of growth hormone therapy. *J Pediatr* 2013;162:263-8.
14. Zanella S, Tauber M, Muscatelli F. Breathing deficits of the Prader-Willi syndrome. *Respir Physiol Neurobiol* 2009;168:119-24.
15. Miano S, Bruni O, Elia M, Musumeci SA, Verrillo E, Ferri R. Sleep breathing and periodic leg movement pattern in Angelman Syndrome: a polysomnographic study. *Clin Neurophysiol* 2005;116:2685-92.
16. Elena G, Bruna C, Benedetta M, Stefania DC, Giuseppe C. Prader-Willi Syndrome: Clinical Aspects. *J Obesity* 2012;1:1-13.
17. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thoracic Soc* 2008;5:136-42.
18. Ronen O, Malhotra A, Pillar G. Influence of gender and age on upper-airway length during development. *Pediatrics* 2007;120:e1028-34.
19. Dancy DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. *Chest* 2001;120:151-5.
20. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children: associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med* 1999;159:1527-32.
21. Camfferman D, Lushington K, O'Donoghue F, Doug McEvoy R. Obstructive sleep apnea syndrome in Prader-Willi Syndrome: an unrecognized and untreated cause of cognitive and behavioral deficits? *Neuropsychol Rev* 2006;16:123-9.
22. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005;353:2034-41.
23. Sedky K, Akhtar U, Oluwabusi O. The ABCDEs of obstructive sleep apnea. *Curr Psychiatry* 2013;12:41-2.
24. Sedky K, Nazir R, Carvalho KS, Lippmann S. Attention deficit hyperactivity disorder and sleep disordered breathing in children. *J Pediatr Biochem* 2013;3:61-7.
25. Yilmaz E, Sedky K, Bennett DS. The Relationship between depressive symptoms and obstructive sleep apnea in pediatric populations: a meta-analysis. *J Clin Sleep Med* 2013;9:1213-20.
26. Sedky K, Carvalho KS, Bennett DS. Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric population: a meta-analysis. *Sleep Med Rev* 2013. <http://dx.doi.org/10.1016/j.smrv.2013.12.003>.
27. Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg* 2009;140:800-8.
28. Schechter MS. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2002;109:e69.
29. Festen DA, Wevers M, de Weerd AW, van den Bossche RA, Duivenvoorden HJ, Hokken-Koelega AC. Cognition and behavior in pre-pubertal children with Prader-Willi syndrome and associations with sleep-related breathing disorders. *Am J Med Genet* 2008;146A:3018-25.
30. Festen DA, de Weerd AW, van den Bossche RA, Joosten K, Hoeve H, Hokken-Koelega AC. Sleep-related breathing disorders in prepubertal children with Prader-Willi syndrome and effects of growth hormone treatment. *J Clin Endocrinol Metab* 2006;91:4911-5.
31. Haqq AM, Stadler DD, Jackson RH, Rosenfeld RG, Purnell JQ, LaFranchi SH. Effects of growth hormone on pulmonary function, sleep quality, behavior, cognition, growth velocity, body composition, and resting energy expenditure in Prader-Willi syndrome. *J Clin Endocrinol Metab* 2003;88:2206-12.
32. Vandenbussche N, de Groen J. Analysis of sleep- and wake disorders in Prader Willi Syndrome. *NSWO* 2007;18:123-6.
33. Harris JC, Allen RP. Is excessive daytime sleepiness characteristic of Prader-Willi syndrome? The effects of weight change. *Arch Pediatr Adolesc Med* 1996;150:1288-93.

34. Hiroe Y, Inoue Y, Higami S, Suto Y, Kawahara R. Relationship between hypersomnia and respiratory disorder during sleep in Prader-Willi syndrome. *Psychiatry Clin Neurosci* 2000;54:323-5.
35. De Cock VC, Diene G, Molinas C, et al. Efficacy of modafinil on excessive daytime sleepiness in Prader-Willi syndrome. *Am J Med Genet* 2011;155:1552-7.
36. Nevsimalova S, Vankova J, Stepanova I, Seemanova E, Mignot E, Nishino S. Hypocretin deficiency in Prader-Willi syndrome. *Eur J Neurol* 2005;12:70-2.
37. Pavone M, Paglietti MG, Petrone A, Crino A, De Vincentiis GC, Cutrera R. Adenotonsillectomy for obstructive sleep apnea in children with Prader-Willi syndrome. *Pediatr Pulmonol* 2006;41:74-9.
38. Meyer SL, Splaingard M, Repaske DR, Zipf W, Atkins J, Jatana K. Outcomes of adenotonsillectomy in patients with prader-willii syndrome. *Arch Otolaryngol Head Neck Surg* 2012;138:1047-51.
39. Tanna N, Choi SS. Efficacy and safety of adenotonsillectomy for pediatric obstructive sleep apnea in Prader-Willi syndrome. *Ann Otol Rhinol Laryngol* 2009;118:267-9.
40. Wong CP, Ng DK, Ma TM, Chau C, Chow PY, Kwok KL. Improvement in quality of life after adenotonsillectomy in a child with Prader Willi syndrome. *Sleep Breath* 2010;14:167-70.
41. Livingston FR, Arens R, Bailey SL, Keens TG, Ward SLD. Hypercapnic arousal responses in Prader-Willi syndrome. *Chest* 1995;108:1627-31.
42. Clinical Advisory Board of the PWS Association, USA. <http://www.pwsausa.org/syndrome/receivaleeppapnea.htm>. Last accessed on October 3, 2013.
43. Uliel S, Tauman R, Greenfeld M, Sivan Y. Normal polysomnographic respiratory values in children and adolescents. *Chest* 2004;125:872-8.
44. Spindelov JS. Assessment of behavioral and psychiatric problems in people with Prader-Willi Syndrome: a review of the literature. *J Policy Pract Intellect Disabil* 2011;8:104-12.
45. Soultan Z, Wadowski S, Rao M, Kravath RE. Effect of treating obstructive sleep apnea by tonsillectomy and/or adenoidectomy on obesity in children. *Arch Pediatr Adolesc Med* 1999;153:33-7.
46. Friedman M, Wilson M, Lin H-C, Chang H-W. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg* 2009;140:800-8.
47. Capdevila OS, Kheirandish-Gozal L, Dayyat E, Gozal D. Pediatric obstructive sleep apnea: complications, management, and long-term outcomes. *Proc Am Thorac Soc* 2008;5:274-82.
48. Kalra M, Inge T, Garcia V, et al. Obstructive sleep apnea in extremely overweight adolescents undergoing bariatric surgery. *Obes Res* 2005;13:1175-9.
49. Won CH, Li KK, Guilleminault C. Surgical treatment of obstructive sleep apnea: upper airway and maxillomandibular surgery. *Proc Am Thorac Soc* 2008;5:193-9.
50. Cohen SR, Holmes RE, Machado L, Magit A. Surgical strategies in the treatment of complex obstructive sleep apnoea in children. *Paediatr Respir Rev* 2002;3:25-35.
51. Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. *Sleep* 2010;33:1457-64.

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