Prader-Willi Syndrome

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Case Vignette

J.R. is a 12-year-old boy with Prader-Willi syndrome who has been followed in a primary care practice. He is referred to you as his developmental pediatrician for evaluation because of inattentiveness, short temper, difficulty following directions, and falling asleep in school. His parents report that he has always been difficult to manage and is "prone to temper tantrums." Although he has never liked school nor done well academically, these problems seem to have escalated over the past school year. His teacher thinks he is sleeping to avoid schoolwork that is difficult for him. Since he reacts to being awakened with tantrums, she is recommending a transfer to a more restrictive school environment, a move his parents oppose.

Your assistant reports that J.R. was asleep in the waiting room and that other children were frightened by loud noises he made as he slept. You review his history and find that he has a long-standing history of snoring, snorting respirations during sleep with witnessed apneas. He is currently receiving growth hormone replacement therapy. Your examination reveals a narrow bifrontal diameter, a high-arched palate, mild micrognathia, dental malocclusion, and 3+ tonsils. His body mass index (BMI) is +3 standard deviations (SD) above the mean for age. The remainder of the examination is noncontributory.

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Introduction to Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a complex neurogenetic disorder originally described in 1956 [1]. The incidence of PWS is estimated to be between 1/10,000 and 1/25,000 live births [2]. However, in infants with hypotonia 0–24 months of age (mean age 8 months), prevalence rates for Prader-Willi syndrome have been reported at 10.7% [3]. PWS results from a silencing of paternally contributed genes on chromosome 15 q11.2–q13. Silencing can result from a frank deletion of the critical region on the paternally contributed member of the pair of chromosomes, a maternal disomy (two copies of maternal chromosome 15, no paternal copy), or rarely, from an imprinting center mutation. This last situation involves a complex genetic mechanism in which a specific region of a chromosome must be "reset" with each generation. In the case of PWS, this reset does not occur in the PWS-specific region of chromosome 15, resulting in the disorder. The diagnosis of Prader-Willi syndrome is made by genetic evaluation. DNA methylation analysis is recommended as the first step in the genetic evaluation of the child with suspected PWS, followed by genetic determination of the causal molecular class, which is important for both genetic counseling and correlation of genotype-phenotype-related concerns [4].

Previously clinicians focused on the clinical phenotype and subsequent course of the disorder, which varies over time. Infancy and early childhood are characterized by infantile hypotonia, often accompanied by feeding difficulties and failure to thrive, an abnormal body composition including a markedly reduced muscle mass, facial and body dysmorphisms, hypogonadism, and developmental issues. Sleep-disordered breathing has been reported across the life span with central apneas occurring more frequently in infants [5, 6]. Between 2 and 3 years of age, significant changes in fat distribution, followed by increased appetite and food intake, emerge, resulting in morbid, and at times, life-threatening obesity [7]. These early concerns are followed by short stature and endocrinopathies. Cognitive

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impairments and characteristic learning difficulties become evident in early childhood, accompanied by emergent behavior difficulties that increase across time, with a particular escalation noted in early adolescence. Behavioral characteristics most often include emotional lability, temper tantrums, stubbornness, compulsivity, and difficulty handling change [8]. Finally, the majority of those affected have hypothalamic-pituitary abnormalities resulting in both growth and sex hormone deficiencies. Until recently, a markedly decreased life span was expected, primarily resulting from obesity-related complications. With improved management, the early introduction of growth hormone replacement therapy and heightened vigilance for, and early treatment of, sleep-disordered breathing, an improved life span, and quality of life, are now evident. Nonetheless, mortality rates in Prader-Willi syndrome, estimated at 3% per year across the age range [9], are still higher than in control individuals who also have an intellectual disability [10].

Case Vignette, Continued

Evaluation of Sleep

J.R.'s history of habitual snoring, witnessed apnea in sleep with associated hypersomnolence, his poor focus, and irritability presents the physician with a high index of suspicion for obstructive sleep apnea. Findings on physical examination support this concern with evidence of obesity, as well as a narrow oropharynx with high-arched palate and enlarged tonsils.

J.R. was referred to a pediatric sleep specialist at a specialty Prader-Willi center who conducted a nocturnal polysomnogram (NPSG or overnight sleep study). The in-laboratory, attended PSG is considered the gold standard for the evaluation of sleep-disordered breathing in children and includes video recording as well as noninvasive monitoring of multiple physiologic variables, including electroencephalography (EEG), pulse oximetry, oronasal airflow, chest and abdominal wall movements, and end-tidal carbon dioxide (CO_2). Specific scoring criteria are available for the interpretation of polysomnograms in children [11].

In this clinical case scenario, the sleep study showed evidence of moderate sleep-disordered breathing (obstructive type), which was noted to be worse during REM sleep. No significant brady- or tachydysrhythmias were reported.

Case Progression

J.R. was referred to a pediatric otolaryngologist (ear, nose, and throat, or ENT doctor) at the center. ENT specialists are important members of multidisciplinary teams at Prader-Willi centers, providing important insights about the anatomy of the upper airway and determining whether surgical options are appropriate for an individual child. J. R.'s examination revealed both enlarged tonsils and adenoids, and he was felt to be an acceptable surgical candidate for adenotonsillectomy, which is often first-line treatment for obstructive sleep apnea (OSA) in children. He underwent a preoperative cardiology evaluation for cor pulmonale, a potential complication of OSA, which was negative; J.R. begun on a weight management program comprised of both exercise and nutrition.

J.R. was admitted to the hospital where he had an uneventful perioperative course and was followed postoperatively by both his surgeon and sleep specialist. He continued to exhibit signs and symptoms of sleep-disordered breathing at his 6-week postoperative visit.

Postoperative assessment with a repeat polysomnogram to evaluate for the presence of residual OSA is indicated for high-risk children such as J.R. who demonstrated a significantly abnormal baseline polysomnogram, obesity, and craniofacial dysmorphology including a high-arched palate, micrognathia, and dental malocclusion, all of which decrease the size of the oropharynx [12]. Therefore, J. R. underwent a postoperative sleep study 8 weeks after his surgery. Despite a mild weight loss and the adenotonsillectomy, the repeat PSG continued to show moderate OSA although the apnea-hypopnea index (AHI) was mildly decreased compared to the preoperative study. A titration study with continuous positive airway pressure (CPAP) was performed with J.R., and an effective pressure was determined. He was started on home CPAP with good results.

CPAP is an effective therapeutic option for children who have objective evidence of OSA following adenotonsillectomy [13]. The CPAP system delivers air under pressure to an airway predisposed to collapse (a common finding in PWS due to upper airway hypotonia), in order to stent open the airway. It can interface with a nasal or full-face mask or nasal pillows. Masks and pillows come in different sizes and are fitted to the individual child. Compliance with using CPAP appliances can be problematic; behavioral interventions may help to improve adherence. It is often helpful to introduce the child to the system prior to starting therapy. Other intervention options, including rapid maxillary expansion, a specialized orthodontic procedure, may be appropriate for selected patients. Weight loss continues to be an important component in the therapeutic plan postoperatively until an appropriate weight is achieved and maintained.

Overview of Sleep-Disordered Breathing with a Focus on Children with Prader-Willi Syndrome

Early reports of Prader-Willi syndrome identified syndrome-specific sleep abnormalities in the form of reduced arousal responses and central apneas, particularly in infants [14], and excessive daytime sleepiness among those school-aged and older. Subsequently, abnormalities of sleep architecture and sleep-disordered breathing, including both oxygen desaturations and obstructive apneas, were identified [15, 16] (Table 16.1). An extensive literature documents an association between sleep disorders and cognitive difficulties, decreased schoolwork performance, and behavior/psychiatric difficulties in the general population. While similar associations are described in individuals with PWS, a sleep-related etiology for behavior challenges is often overlooked within the context of the known marked behavioral difficulties common to this group of children.

Obstructive Sleep Apnea

While children with Prader-Willi syndrome can display a number of complex sleep disorders, affected individuals are especially at risk for developing sleep-disordered breathing with a reported prevalence as high as 89% [17] compared to a 1.2% [18] prevalence reported in the general pediatric population. Obstructive sleep apnea (OSA) constitutes the most common presentation [19]. Predisposing factors for children with Prader-Willi syndrome include craniofacial configuration, hypotonia, increased viscosity of secretions, obesity, and growth hormone therapy [20]. Adenotonsillar size in relationship to a narrower oropharyngeal space is specifically a consideration [21]. Abnormal ventilatory responses to hypoxia and hypercarbia contribute to hypoventilation, augmenting the cardiorespiratory consequences regardless of the cause [22, 23]. While the etiology of the abnormal ventilatory responses remains unclear, the prevailing hypothesis is a dysfunction of the primary peripheral chemoreceptors and/or defective afferent pathways leading to the central controllers [24].

Adenotonsillar hypertrophy is the most common etiologic factor responsible for obstructive sleep apnea in the general pediatric population, whereas among those with Prader-Willi syndrome, the etiology of obstructive apnea is most likely multifactorial.

In the current clinical practice guideline on diagnosis and management of OSA authored by the American Academy of Pediatrics Subcommittee on Obstructive Sleep Apnea Syndrome, OSA is defined as "a disorder of breathing characterized by prolonged partial upper airway and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns and is accompanied by symptoms or signs of OSA" [25].

The preferred testing for the diagnosis of obstructive sleep apnea in children is an attended, in-laboratory nocturnal PSG because it provides an objective and quantitative look at important cardiorespiratory variables during different sleep stages and in different sleep positions, as well as an assessment of sleep patterns. This is a noninvasive procedure and is generally well tolerated by children. During a nocturnal PSG, equipment leads (wires that are placed and temporarily glued to specific locations on the head and body that feed information back to a PSG machine) are placed to determine sleep stages, as well as to monitor nasal and oral airflow, heart rate, respiratory rate, pulse oximetry, and end-tidal CO_2. Overnight polysomnograms are then evaluated against standardized criteria for establishing the diagnosis and classifying the severity of obstructive sleep apnea [26] (Table 16.2). Shorter studies, such as nap studies (PSG monitoring for a time period equal to the duration of a daytime nap), are limited by their failure to provide an opportunity to evaluate all sleep stages; overnight studies using pulse oximetry only are limited by evaluating only one parameter and do not confirm the presence or absence of sleep. Furthermore, oximetry does not address ventilation. Therefore, neither is appropriate for diagnosis of sleep-disordered breathing.

Questionnaires may be helpful in screening children for sleep-disordered breathing; however, current evidence demonstrates that neither patient history nor questionnaires adequately correlate with PSG for the diagnosis of obstructive sleep apnea in children. A 2011 review by Spruyt and Gozal [27] of available pediatric sleep questionnaires found that only the Sleep Disorders Inventory for Students (SDIS) and the Sleep Disturbance Scale for Children (SDSC) fulfilled psychometric criteria. While these tools can complement other components of an assessment, PSG remains the gold standard for diagnosing the presence of OSA as well as for monitoring treatment response.

Table 16.1 Previously identified sleep abnormalities including sleep-disordered breathing in a Prader-Willi syndrome population

Abnormalities of sleep architecture	Decrease in sleep onset
	Decrease in REM latency
	Sleep onset REM periods
	Decrease in NREM sleep instability
	Longer durations of total sleep
Abnormalities of sleep-related breathing	Underarousal
	Abnormal respiratory rate when exposed to hypoxic stimuli
	Central apnea
	Obstructive apnea
	Oxygen desaturations
Other sleep abnormalities	Excessive daytime sleepiness
	Narcolepsy

Table 16.2 Diagnostic and severity classification of obstructive sleep apnea in children

Severity	Apnea index (events/h)	SpO_2 nadir %	$PaCO_2$ Peak (torr)	$ETCO_2$ > 50 Torr (%TST)	EEG arousals (events/h)
Mild	1–4	86–91	>53	10–24	>11
Moderate	5–10	76–85	>60	25–49	>11
Severe	10	≤75	>65	≥50	>11

Modified from Katz and Marcus [26] with permission from Elsevier
EEG electroencephalography, *$ETCO_2$* end-tidal carbon dioxide, *$PaCO_2$* partial pressure of carbon dioxide in arterial blood, *SpO_2* blood oxygen desaturation levels, *TST* total sleep time

Management

Adenotonsillectomy is widely recognized as the treatment of choice for obstructive sleep apnea in children with enlarged tonsils and adenoids who are medically acceptable candidates for surgery. While most children improve with this therapy, outcomes may be less favorable in obese children such as those with PWS [28]. In addition, children with a diagnosis of OSA undergoing adenotonsillectomy have a higher incidence of respiratory complications in the early post-op period as compared to children without OSA [29]. Pavone et al. reported that 4/5 patients with PWS undergoing adenotonsillectomy experienced at least one of the following postoperative complications: delayed emergence from anesthesia, hemorrhage and respiratory complications requiring reintubation, and/or need for supplemental oxygen [30]. In contrast, a later study did not identify significant postoperative complications in this population [31]. It should be kept in mind that both of these studies reported small patient cohorts. These differences may also reflect improvements in anesthesia and surgical management over time and the increased awareness of the special concerns related to children with Prader-Willi syndrome. Late surgical complications may include velopharyngeal/velopalatal insufficiency [32, 33]. It is recommended that children with Prader-Willi syndrome and obstructive sleep apnea requiring adenotonsillectomy be referred to a specialty center with a multidisciplinary team familiar with the syndrome.

Published experience with adenotonsillectomy in children with PWS suggests that while adenotonsillectomy may be effective in most children with PWS and mild to moderate OSA, complete resolution of OSA may not be achieved, especially in those with severe OSA and in those with comorbid obesity [34, 35]. Therefore, follow-up sleep studies are recommended in these high-risk patients at least 6–8 weeks postoperatively under the following circumstances:

- Preoperative diagnosis of moderate or severe OSA
- Sequelae of OSA (e.g., pulmonary hypertension, cor pulmonale)
- Obesity
- Persistent OSA symptoms

Children found to have significant residual apnea on follow-up PSG as well as children who are not surgical candidates should be considered for continuous positive airway pressure (CPAP), a noninvasive ventilatory support system. CPAP stents the pharyngeal soft tissue of the posterior pharyngeal wall, which can lessen or eliminate the obstruction causing the apnea. We recommend that CPAP titrations be performed under the direction and supervision of a pediatric sleep specialist.

Once titrated, adaptation to and compliance with the device is often problematic, especially in children with developmental disabilities and genetic syndromes [36]. Modest benefits have been reported with behavioral interventions [37], including "gradual exposure to CPAP in a supportive setting, as well as anticipatory troubleshooting of typical difficulties and child responses to the challenges of using CPAP" [38]. Overall, however, the current literature is limited regarding successful strategies to improve CPAP compliance in children.

Independent of other treatment interventions, weight loss strategies should be initiated in all children with OSAS who are overweight or obese as there is a clear association between weight loss and improvement in sleep apnea [39]. It must be recognized that affecting weight loss in this population is particularly difficult due to both a reduced metabolic rate and a markedly reduced caloric need in the presence of constant hyperphagia. Thus, weight loss will be slower and more difficult to achieve, although critical.

Additional Sleep Disorders Common in PWS

Excessive daytime sleepiness (EDS) is a frequent finding in individuals with PWS, occurring independent of both BMI and nocturnal sleep status [40]. In studies based on subjective report, the prevalence estimates range from 52% to 100%, with greater prevalence in childhood through the pubertal age, a plateauing in adulthood, and occurring more frequently in those whose PWS results from a paternal deletion [41]. Mimicking narcolepsy, the sleepiness results in naps during rest and inactivity [42]. While the exact mechanism underlying EDS in this population is unclear,

the lack of correlation with other sleep disorders suggests central mechanisms, most likely hypothalamic dysfunction or hypocretin deficiency [43, 44]. Independent of obesity status, central hypersomnolence should be considered in individuals with PWS who fail to respond to either surgery or CPAP and have persistent daytime sleepiness. Modafinil has US Food and Drug Administration (FDA) approval for treatment of sleepiness due to narcolepsy, OSA, and shift work disorder in adults; however, it is not FDA approved for use in children for any indication. Nonetheless, while randomized controlled trials among children with Prader-Willi syndrome and central hypersomnolence are lacking, there are published case reports of successful use of modafinil [45, 46].

Growth Hormone Replacement Therapy and Obstructive Breathing Disorders

Infants and young children with PWS are at higher risk for respiratory difficulties and unexplained sudden death than children without PWS. The etiology of the respiratory problems in PWS seems to be multifactorial in origin but primarily related to insufficiency of respiratory muscles resulting from a genetically driven reduced muscle mass, severe hypotonia, and pharyngeal narrowness [47]. In addition, because of hypotonia-related insufficient airway protection, many infants experience feeding-associated aspiration-induced respiratory problems. While aspiration risks can often be managed by repositioning the infant during and after feeding, nonetheless, the increased risk for respiratory difficulties remains.

The majority of individuals with PWS demonstrate classic growth hormone deficiency even at birth, including reduced muscle mass and strength, low energy expenditure and reduced linear growth even in the presence of obesity, and reduced serum levels of IGF-1 (a serum marker for growth hormone levels). Randomized, controlled studies of growth hormone replacement therapy in the late 1990s documented accelerated growth velocity, increased muscle mass and strength, decreased fat mass, increased physical activity, and even behavior improvements [48–50]. As a result, during the past two decades, growth hormone replacement therapy (GHRT) with daily injectable recombinant human growth hormone has become standard of care for most affected children (and many adults). Crucially, research also demonstrated improved respiratory function [23, 51], even in very young infants treated with GHRT. As a result, in the year 2000, the pharmaceutical companies Pharmacia and Upjohn obtained FDA approval for GHRT for this population. Soon thereafter, there emerged several reports of sudden unexpected death in children with PWS in the early phases of growth hormone treatment [52, 53].

While several theories were hypothesized to explain these deaths, the prevailing etiologic theory centered on GH-mediated tonsillar or soft tissue hypertrophy, increased fluid retention, and soft tissue edema resulting in fatal obstructive sleep apnea. While OSA as a result of GHRT-induced tonsillar hypertrophy previously had been documented in other populations, the available, albeit, sparse evidence in PWS individuals at that point indicated that GHRT improved respiratory function. Further, available data indicated the overall mortality rate of GH-treated PWS patients was lower than that of untreated PWS patients. Nonetheless, the temporal relationship between seven fatal events worldwide and initiation of GHRT led Pharmacia and Upjohn to issue a safety warning on May 30, 2003 [54], indicating that GHRT is contraindicated in patients with PWS who are severely obese or have severe respiratory impairment. This resulted in a number of physicians refusing to or significantly delaying GH treatment to this population.

Subsequently, a number of controlled studies, both cross-sectional and longitudinal, have addressed the following questions:

- Does GHRT raise the risk for OSA in those with PWS?
- What is the increased risk, if any, of sudden unexpected death associated with GHRT?

Collectively, these studies indicate that initiating GHRT does not increase the risk of OSA in *most* individuals affected by PWS. However, there does appear to be an increased risk of obstructive events among those who develop treatment-induced elevated serum IGF-1 levels. Thus, current guidelines recommend a baseline PSG prior to initiating GHRT, especially for those with obesity and hypotonia, with treatment for obstruction as indicated, followed by a repeat PSG 2–6 months after initiation of GHRT and subsequent adjustment of dose if IGF-1 levels exceed two standard deviations greater than the mean for age and gender [55].

Lessons Learned About Sleep Disorders and Prader-Willi Syndrome

- Clinicians should have a high level of vigilance for both sleep-disordered breathing and other sleep disorders in children with Prader-Willi syndrome.
- Routine screening for sleep-disordered breathing is recommended.
- While many sleep questionnaires are available, none is diagnostic.
- The diagnosis of obstructive sleep apnea is made by overnight polysomnogram.

- Adenotonsillectomy is recommended as the first-line treatment in children with PWS and OSA with evidence of adenotonsillar hypertrophy who are deemed acceptable surgical candidates. Residual apnea may be present post-operatively, and follow-up sleep studies are recommended.
- All overweight and obese children with sleep apnea should have weight management and follow-up as part of their treatment plan.

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