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Case Report

# Obstructive Sleep Apnea in Patients with Prader-Willi Syndrome: Unmasking the Hidden Crise!

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## Abstract

Prader-Willi Syndrome (PWS) is a neurobehavioral genetic disease whose cause is failure on chromosome 15. It is characterized by a number of physical, mental, and behavioral anomalies, notably mental retardation, severe hypotonia, hypogonadism, short stature and central obesity. Most of these anomalies create a propitious environment for the development of Sleep-Disordered Breathing (SDB).

The phenotype of SDB evolves over time from predominantly central sleep apnea in infants to Obstructive Sleep Apnea (OSA) in older children. OSA is very common in pediatric patients affected by PWS and causes significant consequences. In this paper, we present two cases of boys with PWS diagnosed with OSA who required the use of Continuous Positive Airway Pressure (CPAP).

**Keywords: Prader-Willi syndrome; Obstructive sleep apnea; Child; Obesity**

## Introduction

Prader-Willi Syndrome (PWS) is a rare genetic disorder caused by loss of function of genes situated within the 15q11-q13 region of chromosome 15. 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 [1]. A delay in diagnosis can occur despite the significant progress made in recent years in understanding the disease. And this is because the clinical features are relatively non-specific and vary with age [2].

The disorder is characterized by hypotonia, developmental delay, hypogonadism, dysfunction of several hypothalamic centers, morbid obesity and psychological problems. These symptoms lead to progressive metabolic, orthopedic, circulatory and respiratory complications. Individuals with PWS are predisposed toward SDB due to a combination of characteristic craniofacial features, anatomically small airways, immature hypothalamic respiratory, hypotonia, and obesity [3].

Rate of OSA among children with PWS range from 44% to 100% [1], suggesting that Polysomnography (PSG) should be performed early to screen for SDB in PWS. Here we review the clinical and sleep study findings in 2 patients with PWS.

## Case Presentation

### Case 1

A 12-year-old male patient was referred to our department with the chief complaint of excessive daytime sleepiness. He is followed in neurology for encephalopathy: generalized hypotonia, sucking disorders and bilateral horizontal nystagmus. The patient underwent a brain MRI and metabolic testing, the results of both of which were normal. His Karyotype was: 45 XY, and there was not a mutation of *FMR1* gene. The patient's mother reported that her pregnancy was uneventful and no other cases have been seen in the family. At anamnesis, marked physical alterations of the syndrome (Figure 1), were noted, such as: obesity, short stature, narrow bifrontal diameter, almond-shaped palpebral fissures, and labial commissures facing down, drooping shoulders, gynaecomastia and small hands. On physical exam, the following findings were observed: Height=140 cm (-1SD, M) and weight=118 kg (>2 SD), with a Body Mass Index (BMI) of 60 kg/m$^2$, indicating severe obesity. Intraoral clinical examination revealed decayed teeth.

During the month preceding his admission, he had consulted psychiatry for violent outbursts which led to the administration of risperidone, but no positive effect was obtained. Behavioral problems persisted: tantrums, impulsivity, stubbornness and aggression. He attended sixth grade primary school; he had poor writing and reading skills. Biological analyzes showed: fasting glucose level, total cholesterol, triglycerides and cortisolemia were within normal limits. Electrocardiogram showed incomplete right bundle branch block

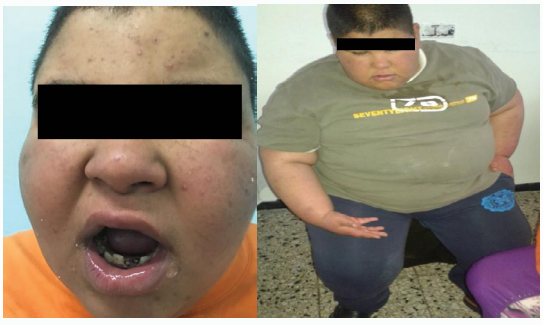

**Figure 1**: Patient's physical characteristics: obesity, short stature, small hands.

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and pulmonary P wave, and a cardiomegaly in the chest radiograph. Therefore, cardiac ultrasound was done showing dilated right cavities with (mPAP) at 57 mmHg and preserved EF. Respiratory polygraphy (Figure 2) was performed and the diagnosis of severe desaturating OSA was retained.

AHI: 52.1/h with a desaturation index at 60/H and an average Sat $O_2$=64.9% (Nadir=51%). Continuous Positive Airway Pressure (CPAP) was indicated but refused by the child with outbursts of anger and agitation. A dietary control was totally rejected. The child died a few weeks after his discharge at the request of the mother.

### Case 2

Case 2 was a 10-year-old boy with a cytogenetic diagnosis of PWS due to a gene deletion. The cytogenetic test was carried out when he was admitted to our department. The patient with low average intelligence was referred for suspicion of OSA: He had a history of loud nocturnal snoring, gurgling during sleep, and nocturia 4 times per night. But he had no nocturnal awakenings or Excessive Daytime Sleepiness (EDS). The pregnancy was uneventful, but the mother recalls very little intrauterine activity. Delivery was full term and uncomplicated. At birth, he was noted to have neonatal hypotonia. He was floppy and weak and, being unable to suck. His testes were not palpable.

During a follow-up he started exhibiting motor delay, achieving sitting at 12 months and walking at 3 years. Later, his speech development was also noted to be compromised and currently he can say only one or two words. During this visit, the parents reported that the patient ate excessively and had an excessive weight gain since the age of 4. The patient was operated on three times for his testicular ectopia and a tonsillectomy at the age of four. Examination findings included a blood pressure of 120 mmHg/60 mmHg, weight of 69 kg (>2 SD), height of 130 cm (+1.5 SD), and BMI of 40.8 kg/m$^2$. Typical features of PWS (Figure 3), such as almond shaped eyes, fish shaped mouth, mild hypotonia, abdominal obesity, marked gynecomastia, and inactive tendon reflexes were observed. His teeth were carious. Small testicles, but normal size external genitalia. Nasal endoscopy showed a remnant of adenoids and free laryngeal airway.

The proband underwent an endocrinological evaluation, which included total serum cholesterol 1.44 gr/L, triglycerides 0.63 gr/L, glucose test pre-meal 0.9 gr/L and TSH 1.92 mIU/L. Cardiac ultrasound was normal (EF=65%) without Cardiovascular shunts. In order to confirm the diagnosis, a polygraph of ventilation was made objectifying a severe OSA (Figure 4), requiring the use of a (CPAP). The patient had an AHI of 20.2 events/hour and an apnea index of 11.4 apneas/h. The average duration of respiratory events is 11 seconds with lowest peripheral oxygen saturation ($SpO_2$) of 28%. From the first moment, he demonstrated interest to use the CPAP.

Continuous dietary intervention and physical activities were also strongly recommended. During the consecutive one-year follow-up our patient showed improvement: an average of weight loss of 4 kg and virtual elimination of snoring. A decision to consider GH therapy after weight loss was taken.

**Figure 2**: Respiratory polygraph tracing of the patient.

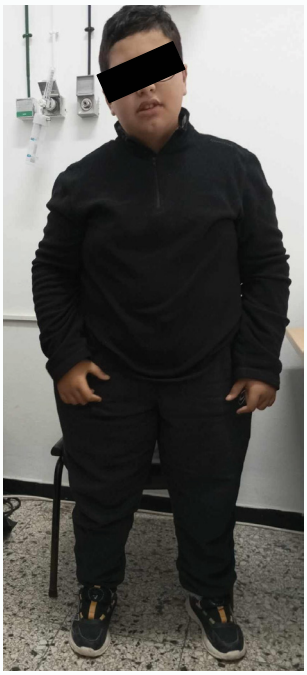

**Figure 3**: Weight loss of patient after one-year follow-up.

**Figure 4**: Polygraph tracing ventilation was made objectifying a severe OSA.

## Discussion

The Prader-Willi Syndrome (PWS) was initially reported in 1956 [4]. It is a complex neurogenetic disorder that occurs in 1 in 10,000 to 1 in 25,000 live births [5]. A deletion on the paternally inherited chromosome 15q11-13 has been demonstrated in 50% to 70% of cases [6]. Features of PWS include hypotonia, hypogonadism and feeding difficulties in infancy [7,8]. The developmental delay becomes apparent in early childhood. Around age 2 years, most affected children develop marked hyperphagia, with consequent morbid obesity, neuroendocrine abnormalities and psychological problems

[7,8]. Emotional lability, obsessive symptoms, hypogonadism, and cognitive impairment are characteristics of PWS in adolescence [8]. People with PWS are at risk of a variety of sleep disturbances. Altered ventilatory control, airway hypotonia, micrognathia, viscous secretions, facial dysmorphism and narrowing of the upper airway make individuals with PWS vulnerable to developing SDB [8-11]. Although the exact prevalence of SDB is difficult to define in people with PWS, but it remains higher compared to the general pediatric population: 80% *vs.* 1% to 30% [3].

The prevalence of those disorders has varied across studies ranging from 44% to 100% [12]. SDB was found in 100% of children with PWS in a recent Indian study [3]. SDB can include both central and OSA, hypersomnolence, narcolepsy, and impaired ventilatory control [5,7]. The peak incidence of Central Sleep Apnea (CSA) is in infancy [7,11]. Contributing mechanisms to CSA are multiple; including hypotonia, scoliosis, brainstem immaturity and hypothalamic dysfunction [3,10,11,13]. Abnormal chemosensitivity to $CO_2$ and $O_2$ may also contribute to hypoxia induced by respiratory depression [13]. Although CSA may gradually improve with maturation, it can also cause to unexpected death.

The actual prevalence of OSA in PWS is difficult to define based on the literature, reflecting selection and the small numbers of patients studied and the selection of the population under study. The peak incidence of OSA occurs at 3 to 6 years, which is similar to the general population [7]. According to recent meta-analysis [10], it is just under 80%, which is much higher than the 1% to 4% prevalence seen in the general pediatric population [1,10]. Given this high prevalence, baseline PSG has been recommended in this population soon after diagnosis, at age 3 years and at the time of puberty [14] to screen for any breathing problems. The Clinical Advisory Board of the PWS Association recommends a PSG study in all PWS children with interpretation by a sleep specialist [1] and per AASM scoring for age [11]. Its prescription must even be accelerated in the event of associated comorbidities such as severe obesity, asthma, Excessive Daytime Sleepiness (EDS), or before an Adenotonsillectomy (AT) or other surgeries requiring sedation [1].

According to a study of 60 adults with PWS, many patients with OSA may not have obvious symptoms, hence the need for ongoing screening and monitoring in this high-risk population [11]. Most studies of children suggest an equal prevalence of OSA by sex. With puberty, a gradual increase in prevalence occurs in men and post-menopausal women due to hormonal changes [1]. Similar to the general population, OSA is significantly correlated with body mass index z-score in children with PWS [7]. And it is typically the upper trunk obesity seen in PWS that plays a major role in the increased load on the respiratory muscles [15]. A neck circumference > 40 cm was defined as a risk factor for sleep apnea [16]. Adenotonsillar hypertrophy may be a contributing factor in young children with PWS, as it is in healthy children. Clinical examination by an otolaryngologist is essential in order to exclude upper respiratory tract abnormalities [4]. Hypothyroidism is a treatable condition sometimes present in children with PWS that may contribute to OSA. Its exact prevalence in PWS patients remains unknown. According to the literature it ranges from 4% to 24% [5,9]. Its screening at the age of 3 months is recommended, and then on an annual basis to supplement a possible deficiency [10].

The OSA assessment includes: echocardiogram looking for pulmonary hypertension (particularly in cases of severe OSA or sleep-related hypoventilation) and screening for gastroesophageal reflux disease, which may worsen OSA [11]. Fifty-three percent of children with PWS had mild forms of OSA, while 22% and 25% were for moderate or severe OSA, respectively [1]. Untreated, OSA causes mortality estimated between 1 and 4% per year and respiratory failure was the leading cause of death for all age groups [11]. It contributes also to a major risk of cardiovascular events: including hypertension, cor pulmonale, and stroke [10] and metabolic diseases like adrenal insufficiency which can cause sudden death [10,11].

Natural resolution of OSA was rare; therefore, therapeutic abstention is not the best strategy to manage them. So, it is necessary to consider aggressive interventions, including: surgical treatment: Adenotonsillectomy (AT), CPAP, earlier in this special group of patients [9]. Adenotonsillar hypertrophy narrows the nasopharynx and oropharynx, which leads to obstruction of the upper airway [7]. Indeed, AT, a mainstay of OSA treatment, can lead to complications. Most common included hemorrhage, respiratory distress, prolonged extubation and Velopharyngeal Insufficiency (VPI) [3,11,14,17].

Furthermore, children with PWS are considered higher than normal risk surgical candidates. Thus, a close monitoring after AT is needed [11]: consider speech evaluations before and after AT, to detect VPI. Additionally, research indicates that repeat PSG should be performed after AT to assess residual OSA [14]. The effectiveness of surgery for OSA in PWS remains unclear to date. Studies evaluating the efficacy of tonsillectomy/adenoidectomy in patients with PWS have shown mixed results. The literature suggests that 60% to 85% of children without facial dysmorphism or genetic abnormalities who have OSA have normal AHI after AT [1]. And according to a meta-analysis [3,18], AT in children with PWS found that 71% of 41 children had a significant reduction in OSA severity, but with residual mild disease. Thus, it is difficult to obtain complete resolution of sleep apnea through AT alone. Other therapeutic alternatives are warranted.

Second-line therapy for OSA is most often CPAP [2,8,10,11,14]. Non-invasive CPAP is a very effective treatment for children refusing surgery, patients without adenotonsillar hypertrophy, or having residual OSA [2,3,8]. It improves EDS, school performance, achievement of developmental milestones and quality of life in patients with severe OSA [9,14]. But, the overall usefulness of CPAP remains limited by their behavioral and learning difficulties and side effects frequently encountered: headache, nasal congestion and mask- or pressure-related discomfort. So, CPAP observance can be challenging. Behavioral therapy is then recommended to facilitate the use of CPAP and should be considered upon initiation of therapy [10,11].

Tracheostomy is rarely used to treat severe cases due to its complications [17]. In 2000, GH became an FDA-approved treatment for people with PWS. Several studies [9,11,14] reported beneficial effects of GH treatment in PWS: namely an increase in growth velocity, stabilize the BMI increment as well as improvement of ventilatory control. Thus, it must be initiated at the time of diagnosis and maintained throughout life [14]. However, GH treatment remains contraindicated in certain situations: severe obesity, untreated severe sleep apnea, acute respiratory disease and active psychosis [11,13]. GH therapy may lead to lymphoid tissue growth, which can exacerbate OSA. Thus, PSG is important prior to initiating GH treatment, and periodically during GH therapy [11]. It also seems prudent to recommend continued observation during GH treatment as patients may not report obvious symptoms of OSA. According to an Australian

multicenter retrospective study [19], there was no significant increase in median OAHI after GH initiation in children with PWS.

Recommendations regarding repeat PSG during GH treatment vary. Current guidelines of the American Academy of Pediatrics recommends that PSG be repeated 6 to 10 weeks after starting GH therapy in children, others have recommended repeating PSG within the first 3-6 months of GH initiation, or as often as once a year during treatment [10,11]. Local corticosteroid therapy (intranasal fluticasone) can be an alternative to CPAP in cases of mild OSA [14]. In case of frequent oxygen desaturations, supplemental oxygen should be prescribed [1]. Weight loss may also be helpful and can lead to improvement of OSA in some patients. Diet and behavioral modifications are usually the first line steps, while laparoscopic sleeve gastrectomy, remains an option still under study [10]. Regardless of the therapeutic option initiated, it is crucial to inform family and to make them responsible for the treatment.

## Conclusion

SDB are prevalent throughout the lifetime of individuals with PWS from infancy to adulthood. They are generally underestimated by parents. Their immediate recognition in this population is of vital importance. OSA remains a common entity in this group. Routine PSG is necessary for its early recognition and should be ideally performed in a sleep laboratory. Optimal care is suggested and should be managed by a multidisciplinary team including endocrinologists, ENT surgeons, sleep specialists and nutrition professionals. Larger studies are needed to determine more specific guidelines and to find the most appropriate therapy and follow-up strategies.

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