Review Article

Respiratory system abnormalities in Prader-Willi syndrome: a literature review

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Background and Objective: Prader-Willi syndrome (PWS) is a genetic disorder characterized by hypotonia and failure to thrive in infancy, followed by hyperphagia and obesity later in life. Phenotypic features include obesity, shot stature, small hands and feet, almond-shaped eyes, and narrow bifrontal diameter. There is multisystem involvement with cognitive, behavioral, and endocrine abnormalities including growth hormone deficiency (GHD), hypogonadism, and obesity from hyperphagia, with its attendant complications of type 2 diabetes mellitus and metabolic syndrome. Additionally, PWS is associated with respiratory system abnormalities due to generalized hypotonia, obesity, and scoliosis that affect the mechanics of respiration, as well as impaired ventilatory and arousal responses to hypercapnia and hypoxia. Respiratory failure is the leading cause of mortality in individuals with PWS, making early diagnosis and the treatment of respiratory problems crucial for their survival. This review summarizes and updates the current knowledge about the mechanisms and screening recommendations for respiratory system abnormalities associated with PWS.

Methods: The only English-language literature search was conducted via PubMed, MeSH, and Google Scholar with keywords that included "Prader-Willi syndrome" and "respiratory" between 1976 and 2021. Additional papers were found via references from articles related to the original search.

Key Content and Findings: A total of 2,111 review articles were identified with keyword "PWS". When we added keywords "respiratory" or "respiratory failure" to PWS, 171 articles were detected. Of those, 74 articles were selected for inclusion based on their relevance to the objectives of this article.

Conclusions: Respiratory system abnormalities in PWS include abnormalities in respiratory control, dysphagia and silent aspiration, abnormal chest wall and pulmonary mechanics, and sleep-disordered breathing. Consideration of the respiratory problems that occur in PWS and the effect of growth hormone treatment (GHT) on these problems contributes significantly to improving prognosis of these individuals. Reports of unexpected mortality with GHT in a subset of PWS patients have raised concerns over safety, though a causal relationship between growth hormone (GH) and sudden death has not been demonstrated. The recommendations are to perform a sleep study, and treat any obstructive sleep apnea (OSA) or respiratory-compromising obesity, prior to initiation of GH.

Keywords: Prader-Willi syndrome (PWS); obstructive and central sleep apnea (OSA and CSA); respiratory failure; mortality

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Introduction

Prader-Willi syndrome (PWS) is a genetic condition resulting from errors in genomic imprinting of the chromosome 15q11-q13 region, most frequently due to a *de novo* paternal deletion of the chromosome (about 60% of cases) leading to a lack of expression of paternally derived genes (1). Maternal uniparental disomy or both chromosome 15s inherited from the mother is seen in about 35% of cases (2,3). Micro-deletions and epimutations in the genomic imprinting center occur in about 3% of cases (2). Rarely, chromosomal translocations or rearrangements of the 15q11-q13 region are reported (3).

PWS affects multiple organ systems and presents with certain clinical features in different growth stages as patients go through a series of nutritional phases (4-7). Significant hypotonia, poor feeding, and failure to thrive occur in infancy. After this period, PWS patients start gaining weight, and between the ages of 3–15 years (with median age of 8 years), there is onset of very aggressive food seeking behavior, reduced satiety and hyperphagia resulting in obesity (7). Obesity is a hallmark feature of PWS, and growth hormone deficiency (GHD) is common with a prevalence ranging from 40–100% based on various studies (8-10). Hypogonadism is also a prominent feature, manifesting as cryptorchidism and micropenis in males (11) and hypoplasia of the external genitalia in females (12). Learning disabilities and mild to moderate intellectual impairment, as well as behavioral issues like skin picking and temper tantrums are common (13).

Despite the vast progress over the past decades in the diagnosis and management, the annual mortality rate of individuals with PWS is still higher than for the general population (14-16). Whittington *et al.* estimated a death rate of 3% per annum in PWS patients compared to that of 1% per annum in the general population (15). One of the largest published cohorts of French PWS registry reported 104 deaths over 11 years. The median age of death was 30 years, ranging from 0–58 years. Respiratory causes accounted for >50% of the mortality, and while respiratory failure was responsible for deaths in adults, respiratory infections were the primary cause of death in children (17). In a series of 64 PWS patients up to 19 years of age, 61% of deaths were due to a respiratory disorder with 44%of these following an upper respiratory tract infection and the remainder due to suffocation or sudden death during sleep, independent of growth hormone treatment (GHT). The median age at death was 3 years (18). The USA PWS Association examined the survival trends in PWS and showed that respiratory failure was the leading cause of death in both males and females, accounting for one-third of all deaths (19).

The pathogenesis of the respiratory problems in PWS seems to be multifactorial in origin, including abnormalities in the control of breathing, swallowing dysfunction and aspiration, respiratory system infections, sleep disordered breathing (SDB), and respiratory failure. Patients with PWS thus need careful otolaryngology, respiratory and dietary evaluation as part of their ongoing management and follow-up.

This review summarizes and updates the current knowledge about the mechanisms and screening recommendations for respiratory system abnormalities associated with PWS. This is pertinent as respiratory infections and respiratory failure are the leading causes of mortality in individuals with PWS, and clinicians need to be aware of risk stratification of patients with respiratory issues prior to initiation of growth hormone (GH) therapy, due to reports of unexpected mortality with GH therapy in a subset of these patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-102/rc).

Methods

Literature search was conducted via PubMed, MeSH, and Google Scholar with keywords that included "Prader-Willi syndrome" and "respiratory" (*Figure 1*). Additional papers were found via references from articles related to the original search. The articles written in English were selected for review (*Table 1*).

Discussion

Respiratory control abnormalities

Regulation of the control of breathing is governed by the central and peripheral chemoreceptors. While central chemoreceptors react to changes in carbon dioxide tension (PCO_2) and hydrogen (H^+) concentration, peripheral chemoreceptors respond to the changes in (PCO_2) and low oxygen partial pressure (PaO_2) levels (20). In mammals, response to hypercapnia and hypoxia is accomplished by increasing the minute ventilation that in turn maintains blood oxygen levels in the normal range. Studies have

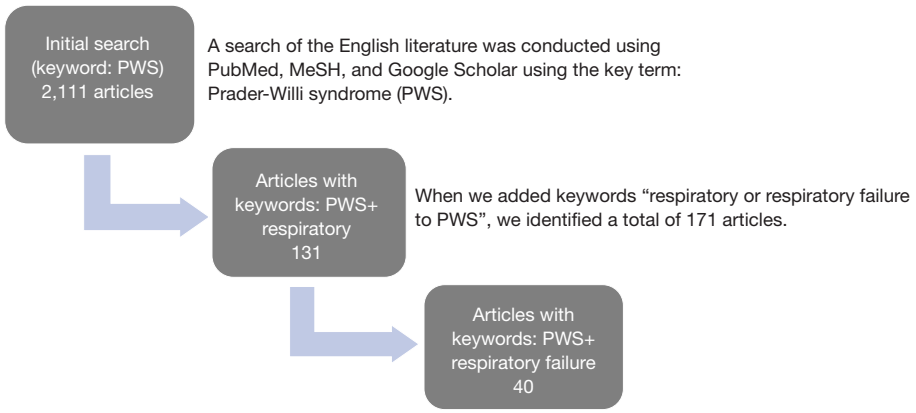

Figure 1 Flowchart depicting the selection process of the articles scrutinized.

Table 1 The search strategy summary

Items	Specification
Date of search	Multiple dates
Databases and other sources searched	PubMed, MeSH, and Google Scholar
Search terms used	PWS
	PWS and respiratory failure
	PWS and GHT
	Central and OSA
Time frame	January 1, 1976, and December 31, 2021
Inclusion and exclusion criteria	Clinical trial
	Meta-analysis
	Randomized controlled trial
	Review
	Systematic review
	Language: English
Selection process	All authors equally conducted the selection, reviewed and agreed with the selected article.

PWS, Prader-Willi Syndrome; GHT, growth hormone treatment; OSA, obstructive sleep apnea.

shown peripheral chemoreceptor function abnormalities in both obese and nonobese patients with PWS (21,22).

Hypoxic ventilatory response (HPVR)

Abnormalities in HPVR have been shown in individuals with PWS. Gozal *et al.* showed that the initial hyperoxic challenge resulted in decrease in minute ventilation in the control subjects but a paradoxical response of increased minute ventilation was observed in subjects with PWS (21). Transient and isocapnic hypoxia challenge during wakefulness resulted in a marked increase in minute ventilation in healthy controls. However, patients with PWS demonstrated absent or reduced ventilatory responses to the same challenge. These observations imply that peripheral chemoreceptor function is affected in both obese and nonobese patients with PWS (21). Another study

showed that individuals with PWS demonstrated abnormal arousal and cardiorespiratory responses to hypoxia (22).

Hypercapnic respiratory response (HCVR)

Hypercapnia is the principal stimulus for the respiratory drive in normal physiological states (23). It has been shown that obese subjects with PWS had a blunted HCVR as opposed to non-obese subjects with PWS and body mass index (BMI)-matched obese controls. This blunted ventilatory response to hypercarbic challenge was attributed to peripheral chemoreceptor dysfunction and/or defect in the afferent pathways projecting to central controllers of breathing (21,22). All these abnormalities in HPVR, HCVR, and arousal response observed in PWS may contribute to morbidity and mortality in these patients. GHT has been shown to improve ventilatory response to hypercarbia and central inspiratory drive in children with PWS (24,25).

Dysphagia/silent aspiration

Infantile hypotonia is a very characteristic feature of PWS and is associated with feeding difficulties during the newborn period (4,7). Most infants with PWS have a weak or uncoordinated swallow that puts them at risk for aspiration (4,26). In general, children with hypotonia may not exhibit the overt, typical symptoms of aspiration such as coughing, gagging, and choking. Subtle signs of "silent" aspiration can be missed, and children may present with apnea, wheezing, or wet cough (27). Recent reports indicate that persons with PWS likely to have an undetected swallowing problem even during adulthood (27,28). A study performed in 30 individuals with PWS between ages of 5–35 years showed that although none of the participants displayed overt signs of dysphagia, majority had abnormal video fluoroscopy swallow study (VFSS) indicating that the dysphagia is subclinical and cannot be detected without formal testing (27). Another retrospective study of 10 infants and toddlers with PWS (age 3 weeks to 29 months) showed a high rate of swallowing dysfunction in the subjects (28). All aspiration events were silent and there were no differences in the rates of aspiration for gender, genetic subtype, or GHT (28). These studies indicate that persons with PWS may present with undetected swallowing dysfunction, even beyond infancy (3). Today, early diagnosis, multidisciplinary care, and GHT have decreased hypotonia, the duration of tube feeding, and dysphagia in children with PWS (3,29,30).

Chest wall and pulmonary mechanics

Hypotonia and respiratory muscle weakness

Hypotonia in PWS presents in utero and is associated with decreased fetal movements and atypical fetal positioning. In the majority of cases, affected newborns are severely hypotonic with depressed reflex activity (4,6). In rare cases, children may present with severe respiratory muscle weakness similar to children with neuromuscular disease complicated with abnormal airway clearance, secretion retention and lower airway infections (26). Later in life, while the hypotonia associated with respiratory muscle weakness alone is usually not severe enough to result in respiratory compromise, when it is coupled with scoliosis and if the ventilatory load is increased secondary to obesity, a restrictive ventilatory defect may present resulting in nocturnal hypoventilation (26,31,32). Although underlying pathogenesis of muscle weakness, and other motor problems in PWS patients is not clear, it is likely that abnormal body composition with an increase in fat mass, decrease in lean body mass (LBM), and some degree of other neuromuscular abnormalities are contributing factors (31,33,34).

Obesity

To maintain the target minute ventilation and compensate the low tidal volume breathing, obese individuals present with a rapid and shallow breathing pattern. They also demonstrate a decreased exercise capacity, a heightened demand for ventilation, elevated work of breathing, and diminished respiratory compliance (35). In obese individuals, conventional respiratory function tests show only mild abnormalities except in extreme cases. The mass loading effect of obesity decreases functional reserve capacity (FRC) while the residual volume (RV) remains normal, leading to decline in expiratory reserve volume (ERV). In obese subjects, accumulation of the fat tissue in the abdomen, around the diaphragm, and ribs decreases the compliance of the respiratory system to the one-third of the normal level (36). In obese children with PWS, alterations in pulmonary function may be more greatly affected due to abnormal body compositions and respiratory muscle weakness which are more prominent in GH naive children (25,26). Early diagnosis, optimal treatment with multidisciplinary care have improved outcomes of individuals with PWS (37). GHT is the major proven intervention for the individuals with PWS and was approved by the US Food and Drug Administration in 2000. Since then, several benefits of GHT have been shown including

increasing height, decreasing body fat, increasing muscle mass, improving weight distribution, increasing physical activity and exercise capacity, and improving bone health (8,38). In addition, GHT has been shown to have a positive effect on development, behavior, cognition and quality of life in PWS (8,30,39).

Sleep and breathing

Individuals with PWS frequently present with a variety of sleep problems, such as central sleep apnea (CSA), obstructive sleep apnea (OSA), alveolar hypoventilation, altered sleep architecture, excessive daytime sleepiness, and narcolepsy-like symptoms (25,26). Individuals with PWS have a high prevalence of sleep related hypoxemia and hypoventilation as well as high respiratory disturbance index (RDI), especially during rapid eye movement (REM) sleep. Comparing to the control subjects with a similar level of obesity, persons with PWS spend more time with low oxygen saturation (SpO_2) levels due to SDB (40). The prevalence of sleep related respiratory events in PWS varies significantly, ranging 41% to 80% (41). There is also an age-related difference in the patterns of SDB in children with PWS. A study performed in GHT naïve infants and children with PWS who did not necessarily have symptoms suggestive of SDB showed that CSA (defined as a central apnea index >5/hour) was common in less than 1 year of age (42). The study also showed that while CSA was uncommon beyond 2 years of age, obstructive events were more common in older children (42). Similarly, another report from China involving 48 children with PWS showed that infants were more likely to have CSA (71.8%) as opposed to older children (25%) who were more likely to have OSA (43).

The Clinical Advisory Board of the PWS Association recommends an overnight polysomnography performed in all children with PWS (5). Today, younger age at diagnosis, multidisciplinary management, and early interventions including GHT have been changing the natural history of PWS and related morbidities including SDB.

CSA

CSA are well recognized in PWS, seems to be more common in children <2 years of age, occur more frequently in REM sleep, and can result in hypoxemia (26,41). The etiology of CSA is likely multifactorial that include poor muscle tone, brainstem immaturity, hypothalamic dysfunction, and altered chemosensitivity to carbon dioxide (CO_2) (25,44). It has been proposed that blunted CO_2 responses in PWS may results in overshooting of HCVR that in turn results in a fall in partial pressure of carbon dioxide ($PaCO_2$) below the eucapnic level and apneic threshold (26). CSA may cause desaturation or be terminated by an arousal and both stimuli may further perpetuate this cycle. It has been shown that oxygen administration significantly improved CSA in children with PWS by eliminating the hypoxia as a precipitating factor and by stabilizing the breathing pattern (45). CSA reported to be more common in PWS individuals with central adrenal insufficiency (44). CSA improves in the majority of infants (73%) beyond 2 years of life, likely due to the maturation of the brainstem by time (41,42).

Necdin, one of a cluster of genes deleted in PWS, may account for respiratory, sensory, motor and behavioral problems associated with PWS. Zanella *et al.* reported that Necdin-deficiency in mice induces central respiratory deficits similar to PWS such as irregular rhythm, frequent apneas, and blunted respiratory regulations (46). Necdin is expressed by medullary serotonergic neurons, and necdin deficiency in neonatal mice alters the serotonergic modulation of the respiratory rhythm generator (47). Studies using genetically altered mice showed that necdin deficiency resulted in serotonergic neuro-structural changes and increased expression and activity of serotonin transporters (47). All these findings support the hypothesis that brainstem serotonopathy is likely part of the pathophysiology of the respiratory and behavioral symptoms of PWS (47).

Although the prevalence of CSA decreases in older subjects with PWS, abnormalities of respiratory control during sleep including blunted ventilatory response to hypercapnia and hypoxia, and poor arousal and cardiorespiratory responses to hypoxia may persist. These deficits may predispose individuals with PWS to developing sleep-related hypoventilation later in life (25). In addition, the abnormal responses to hypoxia and hypercapnia can be exacerbated by obesity. In severe cases, obesity hypoventilation syndrome can develop with significant nocturnal and daytime hypercapnia and these patients may present with symptoms such as hypersomnolence, fatigue or morning headaches and chronic nocturnal hypoxemia can lead to polycythemia and pulmonary hypertension (26). However, today, many people with PWS are not very obese and these extreme conditions are rarely seen in patients who

are receiving guideline based optimal treatments.

OSA

The prevalence of OSA in children with PWS ranges from 44% to 100%, while the rate is 2–3% among healthy children (41,48,49). Individuals with PWS have multiple risk factors for OSA such as craniofacial abnormalities associated with small upper airway caliber, airway obstruction caused by obesity related fat deposition, pharyngeal muscular hypotonia leading to airway collapsibility, and hypertrophic tonsils and adenoids narrowing the airway (42,48). Imaging studies of persons with PWS have shown reduced cross-sectional area at the oropharyngeal or nasopharyngeal level, and although most infants with PWS are not obese, increased airway fat deposition has been demonstrated even in this stage of growth (50). Studies also have shown a varying frequency of central hypothyroidism in PWS from 2–4% to as high as 20–30%, that may be a contributing factor for the sleep related breathing abnormalities (51,52).

In a retrospective report, Pavone *et al.* studied 88 PWS patients (median age 5.1 years) from 3 centers. The prevalence of SDB, defined as apnea hypopnea index (AHI) ≥1.5/h in children and ≥5/h in adults, was 53% in children and 41% in adult subjects. The respiratory events were predominantly obstructive in nature (53). In 30 PWS children from Taiwan (mean age 7.4±4.1 years), the prevalence of SDB, defined by a RDI of >2/hour, was 93%. While 47.4% of the apneas were central, 52.6% were obstructive (54). Sedky *et al.* analyzed fourteen studies of children with PWS who were assessed with polysomnography (n=224). The prevalence of OSA across studies was 79.91%. Among subjects with OSA, 53.07% had mild OSA, 22.35% moderate OSA, and 24.58% severe OSA (48). A prospective study from China enrolled 48 children with PWS. The median age of the children was 16.8 months, ranging between 3–188 months. Overnight polysomnography of these children showed that 87.5% of them had SDB. While 11 (20%) had OSA, 27 (56%) patients had CSA, and 4 patients had both OSA and CSA indicating that while younger children mostly presents with CSA, the prevalence of OSA increases by age (43).

Adenotonsillectomy (AT) is the treatment of choice in children with OSA including those with PWS (49,55). Sedky *et al.* showed that although AT was associated with improvement in OSA for most children with PWS, residual OSA was present in the majority of cases following surgery (48). Two recent metanalysis investigated the outcomes of AT for OSA in children with PWS showed that 20% of patients had complete resolution of OSA (AHI <1.5) and 67% had improvement in the severity of OSA (49,56). They also have found that post op complications of AT were more common (such as velopharyngeal insufficiency) in PWS than non-syndromic children with OSA. These results indicate that although complete resolution of OSA in PWS is not common, many patients benefit from this surgery. Therefore, any patient with PWS and symptoms suggestive of OSA should be evaluated by a polysomnography and referred to otolaryngologist for the surgical management.

SDB and GHT

Early reports of sudden death within first 9 months of GHT have raised concerns about this treatment in PWS (57-60). Initially, it was thought that GHT would worsen the severity of OSA by increasing the soft tissue mass of the airway. However, retrospective reviews of sudden death incidents in individuals with PWS showed that there was no difference in the rates of death who were on or off of GHT (61-63).

GHT improves bone mineral density, body composition, muscle strength, height, and BMI in children with PWS (64). In addition, GHT seems to improve cognitive function and long-term health-related quality of life (39). The FDA recommends GHT at 2 years of age, however, many experts prefers to start GH therapy as early as 2–3 months of age due to its beneficial effects on motor and neurocognitive development (8,39,65).

Several studies investigated the impact of GHT on polysomnography findings of SDB in PWS (66,67). One study involved 62 children aged between 0 and 2.5 years at the beginning of the study. Twenty-one subjects started GHT during the first year of life and 41 after the first year of life (68). Polysomnographic data acquired before and after GHT in regular intervals. There were no significant differences in the RDIs including obstructive apnea hypopnea, central apnea, oxygen desaturation index, and average SpO_2 levels between children who were treated with GH during the first year of life versus the ones received treatment after 1 year of age (68). In an Australian multicenter retrospective analysis, children with PWS investigated with polysomnography before and after introduction of GHT. The study has shown that the median obstructive AHI for the group did not increase significantly after the initiation of GHT. However, 13% of children with no or mild OSA at baseline developed moderate/severe OSA after the initiation of GH therapy (69). Development of OSA could not be explained by changes in body weight

and appeared to be more pronounced in the children under 3 years of age. It is likely that adenoid ± tonsillar tissue hypertrophy which is a common finding in this age group, may have caused OSA in this small percentage of study subjects (70). In this cohort, there was no evidence of a change in CSA with GHT (69).

GHT is currently approved for adults with PWS in a few countries. While the prevalence of OSA in children with PWS has been reported to be as high as 80% (49), the prevalence of moderate to severe OSA has been reported around 22% in adults with PWS (71). A longitudinal prospective study that investigated the effects of GHT on sleep parameters in adults with PWS included thirty-seven adults who were randomly assigned to 1 year of GHT (n=19) or placebo (n=18) followed by 2 years of GHT to all. Each subject underwent polysomnography every 6 months. The study showed a baseline AHI 1.4 (range, 0.0–13.9). There were no differences in sleep or respiratory parameters between GH and placebo-treated patients (72).

A recent report reviewed the published studies of GHT in adults with PWS showed that in most reports the treatment duration was only 1–2 years, except two studies followed patients up to 5 years (73). Although GHT has been shown to help maintain normal body composition and metabolism as well as increased the quality of life, long-term benefits or possible adverse effects of GHT on the respiratory system in adults with PWS need to be investigated further.

Conclusions

Despite the vast progress over the past decades in the diagnosis and management, the annual mortality rate of individuals with PWS is still higher than the general population. Therefore, early diagnosis and multidisciplinary management are crucial for the survival of individuals with PWS. Multiple factors contribute to the respiratory problems seen in PWS, including abnormalities in the control of breathing, swallowing dysfunction and aspiration, respiratory system infections, SDB and respiratory failure. Best practice guidelines recommend a multidisciplinary approach to the diagnosis and management of patients with PWS, including a sleep medicine specialist with expertise of PWS (5,8). GHT is safe and well-tolerated in pediatric population with PWS. The guidelines recommend a polysomnography screening prior to initiating of the GHT, 3–6 months after starting treatment, and then annual screening (8,74). Holding GHT is recommended if there is a concern for development of any type of SDB until it is cleared by an overnight polysomnography (74).

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