



Sleep Disordered Breathing in Prader-Willi Syndrome: A Review

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Abstract

Objectives: PWS is a rare genetic disorder characterized by cognitive impairment, hypogonadism, morbid obesity due to hyperphagia and lack of satiety, and hypothalamic dysfunction. PWS is closely associated with SDB in many forms.

Data sources: A literature search was conducted on the PubMed, MedLine, CINAHL, Embase, Web of Science and Google Scholar databases based on the keywords "Prader Willi Syndrome", "sleep disordered breathing", "obstructive sleep apnea".

Review method: Narrative review of the current literature.

Results: GH therapy was approved in 2000 for treatment of PWS and has been successful in promoting linear growth and improving muscular trophism and tone, with a consequent improvement in strength, physical activity and cardiorespiratory function as well as SDB. However it is not without its complications, in particular sudden deaths. Patients should be managed in the multidisciplinary team with regular polysomnogram especially in the first few weeks following initiation of the treatment. There are other conservative options that can be considered for persistence of SDB despite GH as well as surgical options.

Conclusions: PWS is a rare disorder associated with a variety of SDB. GH has the potential to positively impact on the frequency and severity of SDB in these children. Therefore, they will benefit from careful monitoring in a multidisciplinary setting.

Keywords

Prader-Willi syndrome; Sleep disordered breathing; Children; Growth hormone therapy; Adenotonsillectomy

Introduction

Prader-Willi syndrome (PWS) is a rare genetic disorder classically characterised by cognitive impairment, hypogonadism, morbid obesity due to hyperphagia and lack of satiety, and hypothalamic dysfunction [1-25]. The syndrome was first described by Prader, Labhart and Willi in 1956 [1,3,4,6,7,26,27] and occurs in 1 in 10 000 – 50 000 live births [2-4,8-15,17,22,24,28-31] PWS has an infantile hypotonic phase with feeding difficulties leading to failure to thrive, followed by a childhood obese phase with hyperphagia, developmental delay and hypogonadism [1,2,4,5,14,18,21-23,26-28,32].

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Received: February 17, 2017 Accepted: June 23, 2017 Published: June 30, 2017

PWS is closely associated with sleep disordered breathing (SDB) in many forms, including obstructive sleep apnea (OSA), central sleep apnea (CSA), abnormal arousal, abnormal circadian rhythm of rapid eye movement (REM), and abnormal cardiorespiratory response to hypercapnia [1,2,5,14,16,19-21,25,28,29]. There has been significant advancements in its treatment and a review of these options are presented.

Pathophysiology

OSA is reported to occur in 38-100% of the PWS children at 3 to 6 years old, in contrast to 1-3% of children in the general population [5,14,25,33]. Contributing factors to airway obstruction are thought to include pharyngeal narrowing, facial dysmorphism, viscous secretions, scoliosis, obesity and respiratory muscle hypotonia, which can also contribute to the restrictive lung disease frequently seen in the syndrome [5,13,14,16,20,23,25,30,32-34]. Adenotonsillar hypertrophy may also contribute to airway obstruction [5,16,22,23,25,28,30,32,33,35]. Poor sleep quality, excessive daytime somnolence (EDS) and sedentary behaviour can increase the risk of obesity, which can further exacerbate the upper airway narrowing [16].

CSA in PWS is thought to be due to growth hormone (GH) deficiency, and hypothalamic/pituitary/adrenal dysfunction causing reduced or absent hypoxic and hyperoxic ventilator responses, and hypoarousability, with obesity further blunting this intrinsically abnormal ventilator response to high levels of carbon dioxide (CO₂) [2,8,16,20,28,30,32]. It is reported to be more common in infants [1,5]. They may have a decreased hypoxic ventilatory drive independent of obesity due to altered central and/or peripheral chemosensitivity, with destabilising effect on the control of breathing, resulting in central depression [2,8,32].

Treatment

Growth hormone therapy

GH therapy was approved in 2000 for treatment of PWS. It can now be started before 4 months of age with the advent of improved diagnostic testing [32]. It is successful in promoting linear growth and improving muscular trophism and tone, with a consequent improvement in strength, physical activity and cardiorespiratory function [1-3,7,9,10,12,13,16-19,22,25,27,29,33,36-39]. It can also mediate weight reduction with significant improvement in the ratio between lean body mass and fat mass by stimulating lipolysis, as well as increasing basal metabolic rate [1,2,7,9,12,17,19,25,27,28,32,38]. Some studies suggest its potential to improve cognitive development when started early in life, whereas other studies have failed to demonstrate significant differences [1,11,17,25,27,34,37].

GH has been shown to improve CSA with an increased resting ventilation and central inspiratory drive, as well as increased respiratory response to hypercarbia [13,16,20]. It has been reported to improve OSA as early as after 6 weeks of GH treatment [20].

GH is one of the medical treatment helpful in managing and preventing complications arising from PWS, and thus the potential to improve the SDB. Its use however has been associated with adverse events. It is thought that there is a period of increased vulnerability during the first few weeks following the initiation of GH [1].

The subset of children with worsened obstruction following GH, were obese and had upper respiratory tract infections that did not resolve even after the infective episode [20]. This is thought to be due to chronic upper airway inflammation, which improved with adenotonsillectomy [20]. Gastroesophageal reflux is also reported to be a cause by worsening nasal obstruction [21]. In the short term, the immune system cytokines are stimulated, which may account for the increase in lymphatic tissues size [16]. In addition, IGF-1 mediated hypertrophy of the adenotonsillar tissue may also play a part [7,15,20,29,38]. GH in the short term inappropriately increases plasma renin activity, resulting in water and secondary sodium retention, which may worsen the pre-existing impaired respiration with this volume load [4,20,24]. This may result in cardiac overload and cardiorespiratory impairment, as well as CSF absorption and production mechanism which may affect central functions [16,24]. All these may lead to soft tissue edema, further contributing to upper airway obstruction [15-17,20,24,28,29,39,40].

Although there are concerns that the GH induced accelerated linear growth may influence the incidence or progression of scoliosis, controlled studies have not shown any difference [12,17,18,27,29,34]. It is postulated that the GH mediated increase in muscle mass and strength might decrease its occurrence or progression [27].

PWS children are insulin sensitive due to the predominant subcutaneous deposition of fat, and the reduced counter-regulation of endogenous GH [27]. This may unmask and/or exacerbate glucose intolerance [27]. However, clinically significant changes in measures of insulin resistance or development of glucose intolerance has not been shown [12,27,34].

The overall death rate in PWS not treated with GH in a UK study was calculated to be up to 3% per annum [7,19,21,25,33,41]. This was higher than the 0.13% in the general population [33]. The underlying hypothalamic dysfunction accounts for the increased baseline rates of sudden unexplained deaths: morbid obesity, autonomic instability, reduced ventilator sensitivity to hypoxia and hypercarbia [27]. Infants under one often died of aspiration or hypothalamic dysregulation of respiration; those in early childhood or adolescence from infection; and in adults, complications of morbid obesity [4,7,17,20,29,32,42,43].

Eiholzer et al. first reported the death of a boy 4 months into the GH treatment [4]. In late 2002, there were multiple reports of sudden deaths in children with PWS treated with GH [11,32]. The association is difficult to elucidate with the lack of autopsy and the increased rate of sudden death. Majority of these occurred within 9 months of therapy, usually at night [1,7,20-22,27,28,32,33,44]. Most of these children were under two years old, had an increased OSA severity, were morbidly obese, or suffered from severe respiratory impairment or infection. Respiratory infection, followed by insufficiency is the leading cause of death in PWS, whether they are treated with GH or not, accounting for 68% and 50-55% respectively [7,10,11,22,25,31].

GH is a safe treatment in PWS. Polysomnography and otolaryngology assessments are recommended at baseline and following the start of GH therapy (recommendations varies from 6 weeks to 6 months), or if the patient is symptomatic for SDB [20,32]. These children should be managed in a multidisciplinary approach with close collaborations between the endocrinologists, otolaryngologists and sleep physicians.

Other medical treatments

Studies on pharmacologic agents are limited. There are small reports on the use of mazindol (dopamine reuptake inhibitor), orlistat

(pancreatic lipase inhibitor), sibutramine (noradrenergic reuptake inhibitor), bupropion (activates central melanocortin pathways) and naltrexone (opioid inhibitor) to control appetite and weight, fluoxetine (selective serotonin reuptake inhibitor), to control affective and obsessive symptoms in these children, medroxyprogesterone as a ventilatory stimulant, and stimulants to address the excessive daytime somnolence [13,29].

Obesity is responsible for the primary abnormalities of ventilation in sleep, and weight reduction has been shown to improve OSA and nocturnal hypoventilation [2,13]. This may be achieved with strict dietary restrictions, lifestyle modifications (such as locking food cupboards to prevent food stealing), behavioural and psychological treatment [2,13,29].

Other behavioural management strategies may be employed. PWS children have an increased need for nocturnal sleep, therefore extending sleep time by increasing the time in bed may reduce EDS [13]. Utilisation of more alert periods may maximise participation in exercise and concentration for learning [13].

Other options include oxygen supplementation for nocturnal desaturations, and continuous positive pressure ventilation. These may not be well tolerated in children. The compliance is improved when combined with behavioural interventions. There is limited evidence on the use of dental device in this setting [13].

Surgery

Surgery is the treatment of choice in those with adenotonsillar hypertrophy. Success of adenotonsillectomy in treating children with PWS has been reportedly variable. It has been shown to be beneficial in selected patients with mild to moderate OSA, but some authors also reported benefits in obese ones with severe OSA, bearing in mind that they are high anaesthetic candidates with the concurrent obesity and hypotonia, which may complicate the airway management [7,20,23,26,32,45]. Other common peri-operative problems include difficult venepuncture, disturbance in thermoregulation, diabetes mellitus, arrhythmia and cor pulmonale [26]. Some authors reported that patients can have continued SDB post-operatively due to either residual OSA with snoring or altered respiratory control with more CSA and periodic breathing [32].

Sedky et al. has shown 46.67% of children had normal AHI post-operatively, which is still lower than the 60-85% rate for children in the general population [14]. Meyer et al. reported similar success in obese PWS to those without PWS, with 30-40% not normalising their AHI after adenotonsillectomy regardless of the degree of pre-operative severity [32]. Wong et al. reported not only improvement in the AHI in their patient but also an improvement in the patient's and family's quality of life [46].

Other surgical options include addressing structural abnormalities that may contribute to OSA with nasal surgery, rapid maxillary expansion and mandibular advancement surgeries. These are not well studied in children with PWS. Bariatric surgery has been reported to improve OSA in obese adolescent failing other surgical treatments [14].

Conclusion

PWS is a rare genetic disorder frequently associated with a variety of SDB. Children with PWS present unique challenges in the management of their SDB due to the multi-factorial etiology. GH has been used successfully in the last decade and a half for positively impacting on SDB, but it is not without complications. They would

benefit from careful monitoring of their SDB in a multidisciplinary setting, with medical and surgical treatments tailored to their individual needs.

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