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.
Study Design: Narrative review.
Methods: 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.

Introduction

- Prader-Willi syndrome (PWS) is a rare genetic disorder classically characterised by cognitive impairment, hypogonadism, morbid obesity due to hyperphagia & lack of satiety, & hypothalamic dysfunction.
- The syndrome was first described by Prader, Labhart & Willi in 1956 and occurs in 1 in 10000-50000 live births.
- PWS has an infantile hypotonic phase with feeding difficulties leading to failure to thrive, followed by a childhood obese phase with hyperphagia, developmental delay & hypogonadism.
- PWS is closely associated with sleep disordered breathing (SDB), including obstructive sleep apnea (OSA), central sleep apnea (CSA), abnormal arousal, abnormal circadian rhythm of rapid eye movement (REM), & abnormal cardiorespiratory response to hypercapnia.
- 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 3-6yo, in contrast to 1-3% in the general population.
- Contributing factors to airway obstruction include adenotonsillar hypertrophy, pharyngeal narrowing, facial dysmorphism, viscous secretions, scoliosis, obesity & respiratory muscle hypotonia, which may contribute to the restrictive lung disease frequently seen in PWS.
- Poor sleep quality, excessive daytime somnolence (EDS) & sedentary behaviour may lead to obesity, which further exacerbate the upper airway narrowing.
- CSA in PWS is thought to be due to growth hormone (GH) deficiency, & hypothalamic/pituitary/adrenal dysfunction causing reduced or absent hypoxic & hyperoxic ventilator responses & hypoarousability, with obesity further blunting this intrinsically abnormal ventilator response to high levels CO_2.

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Treatment

Growth Hormone Therapy

- GH therapy was approved in 2000 for treatment of PWS. It can be started <4-month-old with the advent of improved diagnostic testing.

Growth	Linear growth Muscular trophism & tone	⇨ Improves strength, physical activity & cardiovascular function
Weight reduction	Lipolysis ↑ Basal metabolic rate	
OSA Effects	Improvement as early as after 6w due to the above	
Neurological	May improve cognitive development when started early in life	
CSA Effects	↑ Resting ventilation & central inspiratory drive ↑ Respiratory response to hypercarbia	

Table 1: Benefits of GH therapy

- GH is helpful in managing & preventing complications arising from PWS.
- 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.

Worsened Obstruction	Obese children with URTI that did not resolve: • Due to chronic upper airway inflammation, improved with adenotonsillectomy • GORD worsens nasal obstruction • Immune system cytokine stimulation → Lymphatic tissue hypertrophy
Impaired Respiration	↑ Plasma renin activity → H_2O & Na^+ retention Volume overload → Cardiac overload: • Cardiorespiratory impairment • CSF absorption & production → Affect central functions Soft tissue edema exacerbating airway obstruction
Death Rate	3% vs 0.13% in general population due to underlying hypothalamic dysfunction (Morbid obesity, autonomic instability & ↓ ventilator sensitivity to hypoxia & hypercarbia) • <1yo: often died of aspiration/hypothalamic dysregulation of respiration • Early childhood/adolescence: Infection • Adults: Complications of morbid obesity

The association is difficult to elucidate with the lack of autopsy & ↑ sudden death. Majority of these occurred within 9m of therapy, usually at night. Most were <2yo, with ↑ OSA severity, were morbidly obese, or suffered from severe respiratory impairment/infection. Respiratory infection, followed by insufficiency is the leading cause of death in PWS, with or without GH (68% and 50-55% respectively)

Table 2: Complications of GH therapy

- 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.
- Clinically significant changes in insulin resistance/glucose intolerance has not been shown despite them being insulin sensitive due to subcutaneous fat & ↓ counter-regulation of endogenous GH.
- GH is a safe treatment in PWS.
- Polysomnography & otolaryngology assessments are recommended at baseline, & following the start of therapy, or if patient is symptomatic for SDB.
- They 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:

Small reports for appetite & weight control	Mazindol (dopamine reuptake inhibitor Orlistat (pancreatic lipase inhibitor) Sibutramine (Noradrenergic reuptake inhibitor) Bupropion (Activates central melanocortin pathways) Naltrexone (Opioid inhibitor)
Small reports for affective & obsessive symptom control	Fluoxetine (SSRI)
Ventilatory stimulant	Medroxyprogesterone

Table 3: Other medical treatments

- Weight reduction has been shown to improve OSA & nocturnal hypoventilation.
- This may be achieved with strict dietary restrictions, lifestyle modifications (such as locking food cupboards to prevent food stealing), behavioural & psychological treatment.
- Other behavioural management strategies may be employed: Extending sleep time may ↓ EDS; alert period utilisation to maximise exercise & learning.
- Other options: Oxygen supplementation & CPAP but may not be well tolerated. There is limited evidence on the use of dental device in this setting.

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-moderate OSA, but some also reported benefits in obese ones with severe OSA (bearing in mind that they are high anaesthetic candidates).

Peri-Operative	Airway management: • Obesity & hypotonia Difficult venous access Thermoregulation disturbances Cardiorespiratory: • Arrhythmia • Cor pulmonale Metabolic: Diabetes mellitus
Intra-Operative	As above
Post-Operative	Persistent SDB: • Residual OSA with snoring • Residual CSA with altered respiratory control

Table 4: Potential surgical complications

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

Conclusions

- PWs is a rare genetic disorder frequently associated with a variety of SBD.
- Children with PWS presents unique challenges in the management of their SDB due to the multi-factorial etiology.
- GH has been used successfully in the last decade & 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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