**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 hypophagia and lack of satiety, and hypothalamic dysfunctions. 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 tropism 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 overnight polysomnography 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.

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**Introduction**

- Prader-Willi syndrome (PWS) is a rare genetic disorder classically characterized by cognitive impairment, hypogonadism, morbid obesity due to hypophagia & lack of satiety, & hypothalamic dysfunctions.
- 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 hypophagia, 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 hypocapnia.
- There has been significant advancements in its treatment and a review of these options are presented.

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**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 dysmorphosis, 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 & hypoarousalability, with obesity further blunting this intrinsically abnormal ventilator response to high levels CO₂.

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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 tropism & tone
- Improves strength, physical activity & cardiorespiratory 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 hypercapnia

**Worsened Obstruction**
- Obese children with URTI that did not resolve:
  - Due to chronic upper airway inflammation, improved with adenosinotolloyctomy
  - GORD worsens nasal obstruction
  - Immune system cytokine stimulation → Lymphatic tissue hypertrophy

**Impaired Respiration**
- Plasma renin activity → H₂O & Na⁺ retention
- Volume load → 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 & hypercapnia)
- <1yo: often died of aspiration/hypothalamic deregulation of respiration
- Early childhood/adolescence: Infection
- Adults: Complications of morbid obesity

**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)
    - Buproprion (Activates central melanocortin pathways)
    - Naltrexone (Opioid inhibitor)
  - Small reports for affective & obsessive symptom control
    - Fluoxetine (SSRI)
    - Venlafaxine (SNRI)
    - Medroxyprogesterone

**Table 3: Other medical treatments**

- Weight reduction has been shown to improve OSA & nocturnal hyperventilation.
- 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 ↓ 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.

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**References**