Presentations and Management of Sleep Disorders in Prader Willi syndrome

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Learning Objectives

Utilize case-based learning to discuss presentations of sleep disorders in PWS

Consider diagnostic evaluation.

Consider presentations that masquerade as other manifestations of PWS.

Review treatment strategies for sleep disorders in PWS.

Case 1

10 -male with Prader Willi syndrome is often noted to fall asleep at school. If he is awakened, he is very irritable, can escalate behaviors very quickly and even become aggressive. He is quick to get frustrated and angry sometimes around food, but other times it could be over anything, and the triggers may be unclear. He will sleep anywhere, especially on car rides.

Excessive Daytime sleepiness (EDS)

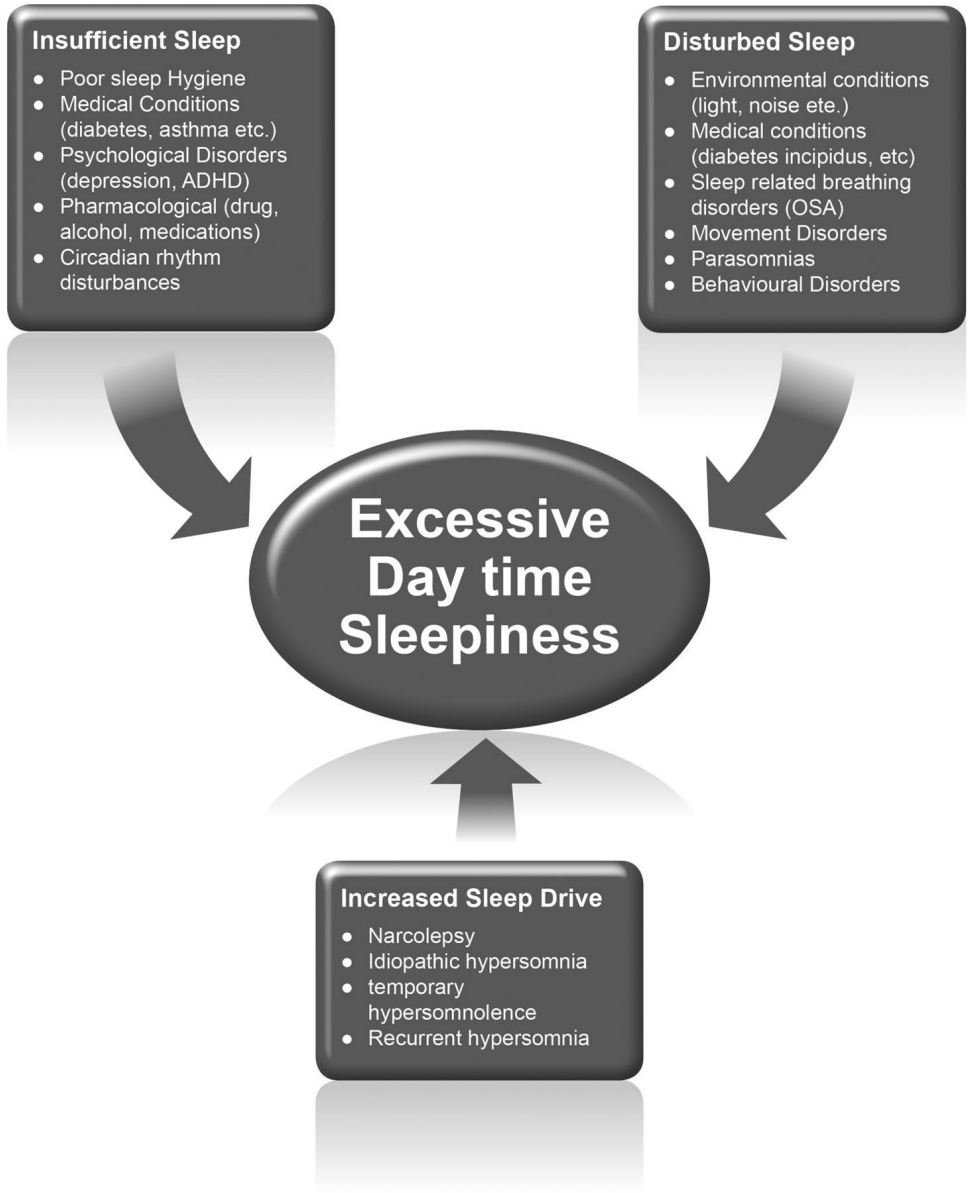
- Decreased wakefulness with an increased % of sleep time and stage N3 sleep during the day and night
- May be part of the initial clinical phenotype at birth when individuals with PWS are excessively sleepy and often fall asleep during feeding
- 67% of adults report EDS
- May be confounded by obstructive sleep apnea
- Commonly presents with irritability and behavioral disturbances

Ghergan A, Coupaye M, Leu-Semenescu S, et al. Prevalence and Phenotype of Sleep Disorders in 60 Adults With Prader-Willi Syndrome. Sleep 2017;40(12) (In eng). DOI: 10.1093/sleep/zsx162.

Vgontzas AN, Kales A, Selp J, et al. Relationship of sleep abnormalities to patient genotypes in Prader-Willi syndrome. Am J Med Genet 1996;67(5):478-82. DOI: 10.1002/(SICI)1096-8628(19960920)67:53.0.CO;2-G.

Harris JC, Allen RP. Is excessive daytime sleepiness characteristic of Prader-Willi syndrome? The effects of weight change. Arch Pediatr Adolesc Med 1996;150(12):1288-93. DOI: 10.1001/archpedi.1996.02170370066011.

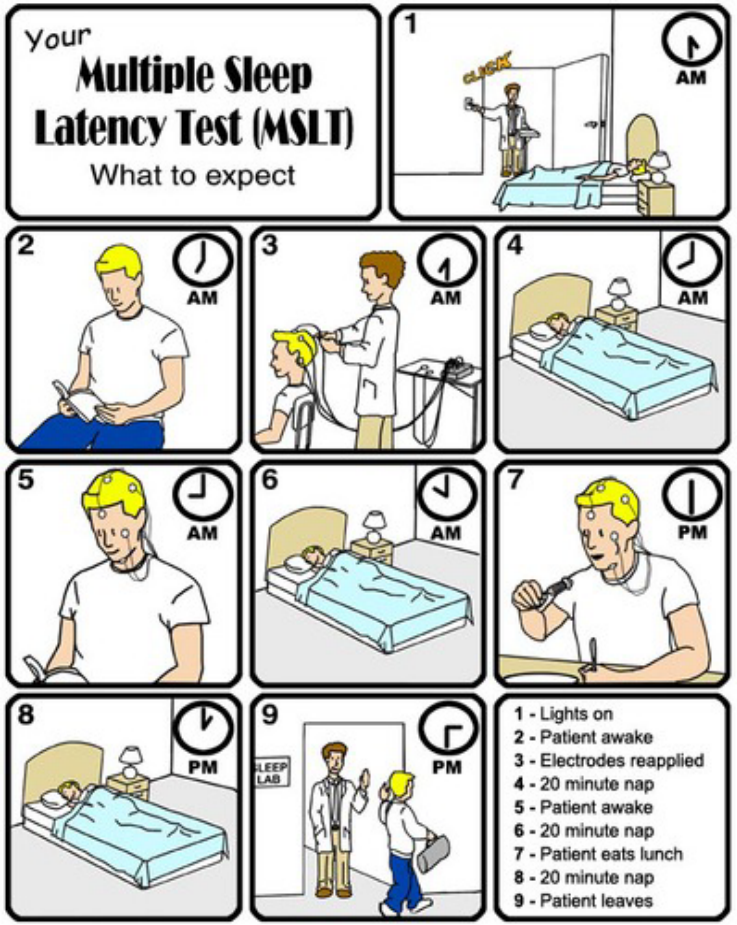
EDS disrupts school performance and may be associated with irritability and behavioral disturbances commonly seen in individuals with PWS.



Kallambella K, Hussain N. Approach to a child with excessive daytime sleepiness *Archives of Disease in Childhood - Education and Practice* 2015;**100:**288-294.

Even in individuals with an established diagnosis of OSA, the correlation of apnea-hypopnea index (AHI) with EDS reveals an out-of-proportion finding suggestive of EDS.

Picture 1: Having a sleep study

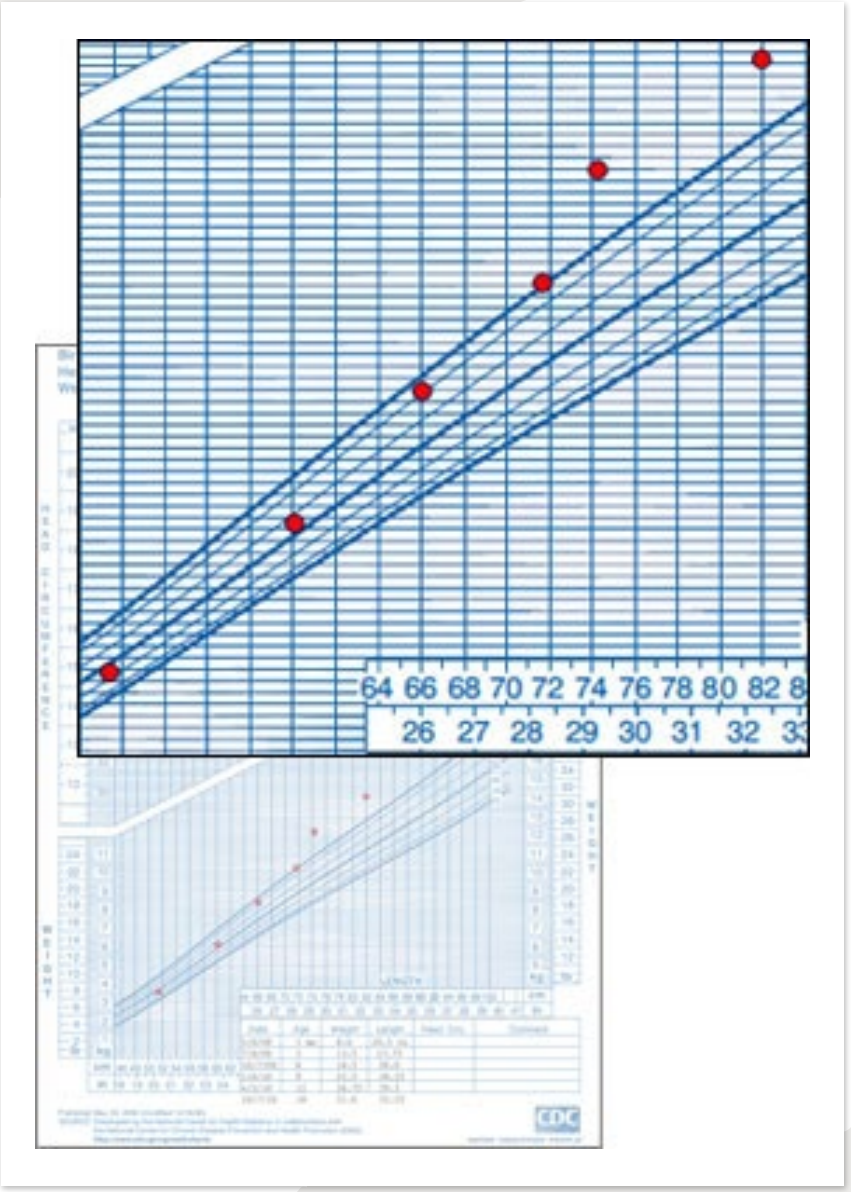


Treatment of EDS in PWS

Treatment	Description	References
Modafinil	In 10 patients studied ages 8-21 years with PWS, modafinil was shown to decrease sleepiness.	Lee YJ, Marcu S, Berall G, Shapiro CM. Tryptophan for the treatment of excessive daytime sleepiness in Prader-Willi syndrome. Indian Pediatr 2011;48(4):319-21. DOI: 10.1007/s13312-011-0053-6
Clomipramine	EDS was successfully reduced in an 11-year-old boy with PWS when treated with clomipramine. He experienced a slight improvement in nocturnal hypoxemia though his OSA persisted.	Esnault-Lavandier S, Mabin D. [The effects of clomipramine on diurnal sleepiness and respiratory parameters in a a case of Prader-Willi syndrome]. Neurophysiol Clin 1998;28(6):521-5. DOI: 10.1016/s0987-7053(99)80020-3.
Tryptophan	8-year-old girl with PWS and EDS was successfully treated with tryptophan.	Lee YJ, Marcu S, Berall G, Shapiro CM. Tryptophan for the treatment of excessive daytime sleepiness in Prader-Willi syndrome. Indian Pediatr 2011;48(4):319-21. DOI: 10.1007/s13312-011-0053-6.
Pitolisant	Reduction in sleepiness and improvement in cognitive function in case reports of children with PWS.	P L, Picone M, Tan L, Johnston C, Stark H. Pitolisant Is A Safe And Effective Treatment For Children With Prader-willi Syndrome (pws). Sleep 2019;42:A309-A310. DOI: 10.1093/sleep/zsz067.769. Pullen LC, Picone M, Tan L, Johnston C, Stark H. Cognitive Improvements in Children with Prader-Willi Syndrome Following Pitolisant Treatment-Patient Reports. J Pediatr Pharmacol Ther 2019;24(2):166-171. DOI: 10.5863/1551-6776-24.2.166.

Case 2

- An 8 year with recent excessive weight gain presents with irritability, excessive sleepiness, increased food seeking including awakening and foraging for food at night, worsening school performance, and headaches. Parents have recently noted more snoring especially when ill.



Obstructive sleep apnea is common in PWS.

More than 80% of individuals with PWS exhibit sleep disordered breathing including OSA

Percentile of BMI for the individuals' age and sex has been associated with more severe hypoxemia during sleep and more sleep disruptions.

Untreated OSA has been associated with more severely delayed developmental milestones.

Worsening OSA has also been associated with EDS and autistic-related behavior with worsening impulsivity.

Behavioral changes should prompt concern for worsening OSA. In addition, developmental milestones may be more severely delayed in individuals with untreated OSA.

Diagnostic work up

Diagnosis of OSA is via polysomnography.

Drug-induced sleep endoscopy should be performed when an infant is diagnosed with OSA prior to the development of tonsils and adenoids (Evidence Level 1b).

Treatment of OSA

- Referral to otolaryngology (ENT)
- Oxygen for hypoxemia and sometimes if adherence to other treatments are low
- CPAP
- Behavioral therapy with desensitization to assist in use of CPAP should be considered upon initiation of therapy.
- In the case of mild OSA, a trial of intranasal fluticasone with or without montelukast can be used as an alternative to CPAP.
- In cases where PAP therapy fails, consider Optiflow nasal high flow therapy (NHF)

	NHF	CPAP
		
Control	**Flow-based control** (with varying pressure)	**Pressure-based control** (with varying flow)
Unit of measure (used for therapy settings)	**L/min**	**cmH_2O**

Growth Hormone and OSA

Current recommendations include monitoring for symptoms of OSA before initiation and while continuing GH therapy.

Obtaining a PSG should not delay initiation of GH therapy.

Approximately 6-10 weeks post-initiation of GH, a follow-up sleep study may be needed if any worsening symptoms (such as but not limited to snoring, witnessed apnea, daytime sleepiness) or signs (such as but not limited to weight gain) occur.

Findings of worsening obstructive apnea-hypopnea index (OAHI) should expedite evaluation and treatment, but not stop or delay GH treatment.

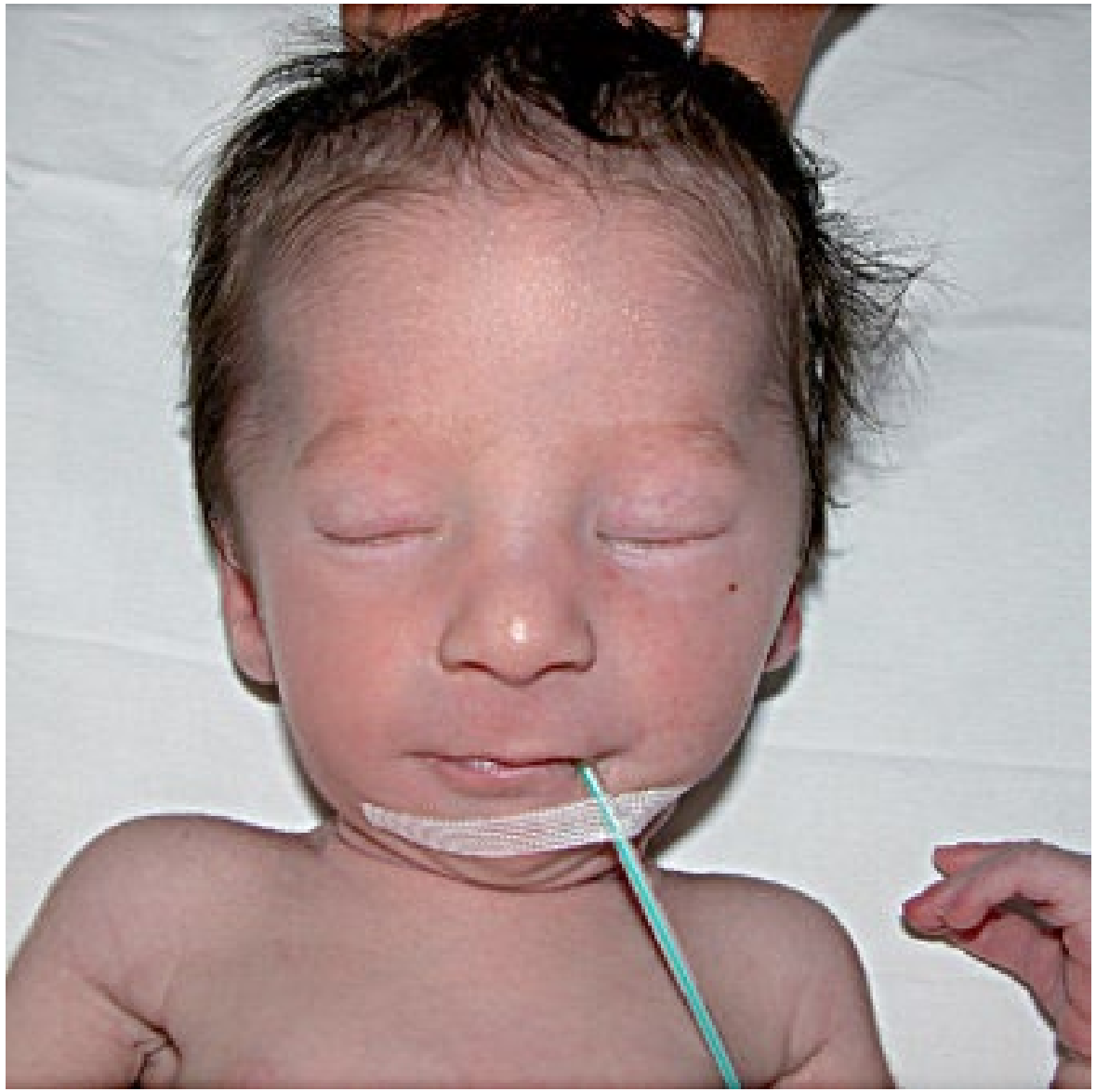
Clinical management of patients on GH who are diagnosed with OSA remains highly variable among endocrinologists and sleep specialists across medical centers.

Snoring, witnessed apneas, rapid weight gain, change in school performance, new onset attention concerns, worsening EDS, more irritability or change in behavior, or lack of progression in development should prompt a referral for PSG.

In addition, routine PSG should be performed at age 3 years and at the time of puberty in children with PWS

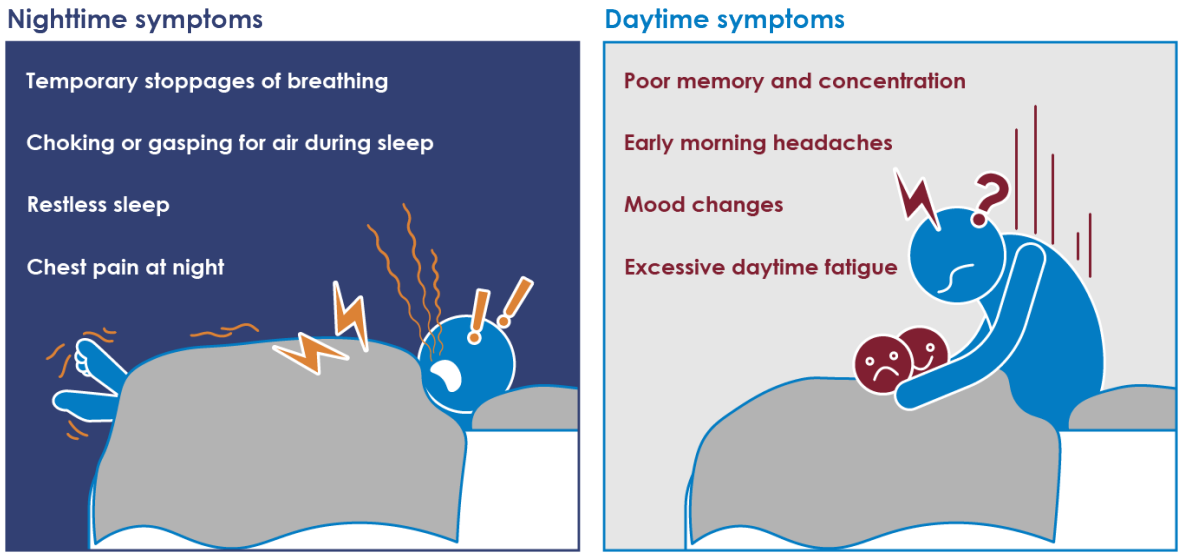
Case 3

- Newborn infant in the NICU is noted to have apneic events, followed by bradycardia. She is noted to have low muscle tone and poor interest in feeding. Testing is pending.



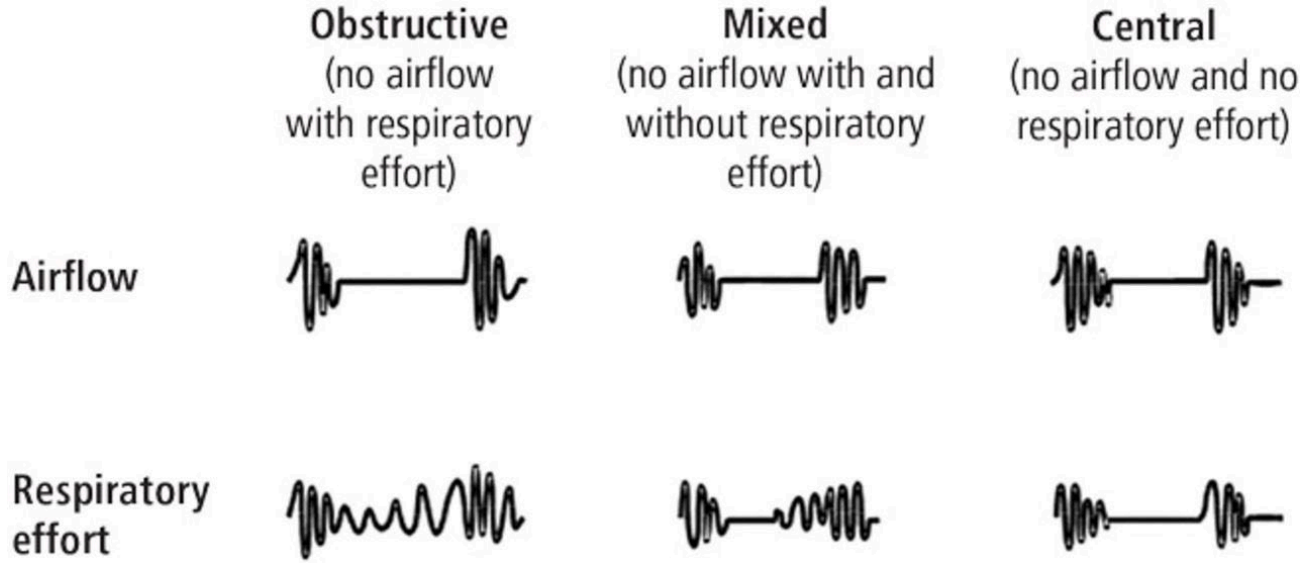
Corsello, Giovanni & Giuffrè, Mario. (2012). Congenital Malformations and Syndromes: Early Diagnosis and Prognosis. 10.1007/978-88-470-1405-3_6.

Central Sleep apnea



https://www.medthority.com/specialty/respiratory/

Diagnosis of Central Sleep Apnea on PSG



Cleveland Clinic Journal of Medicine September 2019, 86 (9 suppl 1) 2-9; DOI: https://doi.org/10.3949/ccjm.86.s1.02

Screening/Treatment of CSA

Rule out central adrenal insufficiency

Continued monitoring with frequent PSGs approximately every 6 months may be indicated for these individuals with central adrenal insufficiency.

Supplemental oxygen has been shown to be an effective treatment in infants and is the therapy of choice for this age group.

For older individuals, the use of positive airway pressure is the standard of care.

Case 4

- A 6-year-old with PWS presents with history of concerns for seizures (ruled out with EEG in the past) described as loss of tone during eating. More recently she has been falling asleep sometimes midsentence. The school is concerned about a change in her performance recently. If she is awakened from sleep at school she gets very angry and emotional. After seeming to regain her energy she falls immediately back asleep after having a behavioral outburst. A recent sleep study shows mild OSA for which ENT recommended flonase. Her level of sleepiness is out of proportion to her mild OSA. Parents come to clinic concerned about regression due to seizures.

Narcolepsy and Cataplexy Presenting Features

NARCOLEPSY	CATAPLEXY
Children can have profound baseline facial hypotonia and some patients experience motor tics.	May resemble clonic, atonic, and/or myoclonic seizures; however, the loss of consciousness is absent with cataplexy
Automatic behavior (repetitive and common behaviors done at night)	Loss of tone and or/complex hyperkinetic movements
Disrupted nighttime sleep	Facial involvement that can include active movement of the tongue and perioral muscles
Obesity is also common in children with narcolepsy such that more than half of children who first present with signs of narcolepsy are obese	Children may experience cataplexy without a clear emotional trigger
Approximately one third of children with narcolepsy also have symptoms of attention deficit hyperactivity disorder or behavior concerns	Cataplexy or sudden onset of atonia provoked by emotion appears relatively commonly in PWS; e.g., head drops in young children as they eat solid food is likely an example of cataplexy in PWS

Consensus statement on work up for narcolepsy/cataplexy

"Since a diagnosis of narcolepsy also requires that a patient's EDS is not caused by insufficient sleep or another sleep disorder, such as OSA, it can be difficult to obtain a formal diagnosis of narcolepsy in PWS. Often patients with PWS and OSA have difficulty adhering to their prescribed positive airway pressure (mainly CPAP or bilevel positive airway pressure (BPAP) therapy). This means that, per clinical guidelines, OSA cannot be excluded as a cause of their excessive daytime sleepiness. This situation may contribute to the underdiagnosis of narcolepsy in the PWS population. Because EDS is often out of proportion to OSA, we recommend that screening for narcolepsy type features should be undertaken in individuals with PWS despite residual OSA."

Duis J, Pullen LC, Picone M, Friedman N, Hawkins S, Sannar E, Pfalzer AC, Shelton AR, Singh D, Zee PC, Glaze DG, Revana A. Diagnosis and management of sleep disorders in Prader-Willi syndrome. J Clin Sleep Med. 2022 Jun 1;18(6):1687-1696. doi: 10.5664/jcsm.9938. PMID: 35172921; PMCID: PMC9163612.

Treatment of narcolepsy in PWS

Amphetamine/methylphenidate

Modafinil

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) may be used to treat cataplexy*

Sodium oxybate, the sodium salt of gamma hydroxybutyrate**

Pitolisant

*caution due to potential for activation in individuals with PWS

**Sodium oxybate is the drug of choice for narcolepsy Type 1 in children and adults. Use of sodium oxybate may cause respiratory depression and should be approached with much caution in this population. A clinical trial in PWS would be indicated before consideration of use.

Other disorders to be aware of in PWS

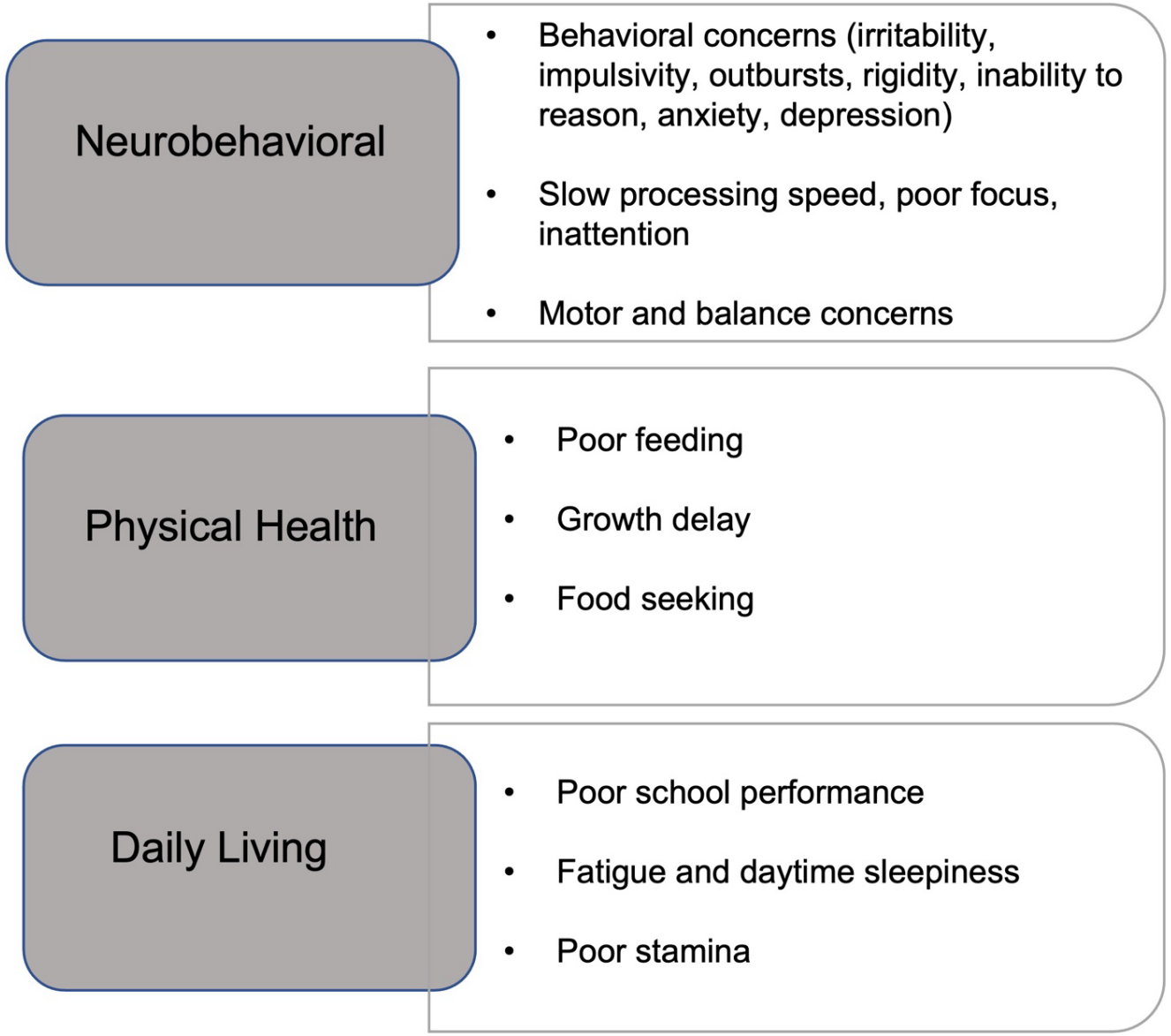
Chronic insomnia

- Consider food seeking, behavioral concerns, anxiety, or perseverative behaviors that could be impacting sleep
- Referral to sleep specialist
- Consider behavioral therapy
- Improve food security in the home to decrease anxiety and access

Restless leg m

- A recent Cochrane review found that iron supplementation probably improves restlessness and restless leg syndrome severity in comparison to placebo. Importantly, benefits were seen even when participants did not have low blood levels of iron
- Consider checking serum ferritin.
- With iron therapy, consider risks of constipation and monitor ferritin to ensure appropriate dosing. Also ensure iron is stored safely in a locked cabinet in the home as an acute overdose may be fatal.

Symptoms to Consider as Related to sleep disorders in PWS



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All PWS patients

Prior to the initiation of growth hormone (GH), physicians should consider a sleep study. This testing should not delay initiation of GH.

All patients with Prader-Willi syndrome (PWS) should be evaluated at least annually for sleep disorders including sleep disordered breathing, excessive daytime sleepiness (EDS), narcolepsy, cataplexy, and insomnia.

PWS patients could benefit from having sleep specialists included in their multidisciplinary medical team because sleep problems are complex and common in this population.

Consider the role of sleep disorders in behavioral problems and food seeking at night.

Diagnosis

Change in weight across 1-2 percentiles, rapid weight gain, change in school performance, new onset attention concerns, worsening EDS, more irritability or change in behavior, or lack of progression in development, or change in school performance should prompt a referral for comprehensive sleep evaluation

Polysomnography (PSG) is indicated for evaluation of sleep disordered breathing.

Sleep diary and actigraphy with overnight PSG followed by the multiple sleep latency test (MSLT) should be considered for evaluation of EDS.

When EDS is out of proportion to level of control of obstructive sleep apnea (OSA), an assessment using MSLT should be considered.

Treatment

Consider using currently accepted guidelines for treating identified sleep disorders in consultation with sleep specialists. To date no therapies have been established for EDS, narcolepsy, cataplexy, and insomnia in PWS.

Consider the practice parameters for narcolepsy when treating patients with PWS who have EDS.

Duis J, Pullen LC, Picone M, Friedman N, Hawkins S, Sannar E, Pfalzer AC, Shelton AR, Singh D, Zee PC, Glaze DG, Revana A. Diagnosis and management of sleep disorders in Prader-Willi syndrome. J Clin Sleep Med. 2022 Jun 1;18(6):1687-1696. doi: 10.5664/jcsm.9938. PMID: 35172921; PMCID: PMC9163612.

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Thank you

- Questions?