CME

Prader-Willi Syndrome and Sleep-Disordered Breathing

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Abstract

Prader-Willi Syndrome is a complex neurogenetic disorder characterized by appetite dysregulation, obesity with decreased muscle mass and increased fat mass, behavioral problems, various endocrinopathies, and sleep and respiratory abnormalities. Respiratory issues include both central and obstructive sleep apnea, excessive daytime sleepiness, narcolepsy, and impaired ventilatory control. There is some controversy as to whether growth hormone treatment, which is the standard of care for patients with Prader-Willi Syndrome, exacerbates or ameliorates the sleep-disordered breathing issues associated with this syndrome. The natural history of sleep and breathing issues and the issues surrounding growth hormone treatment on sleep-disordered breathing are discussed.

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CME EDUCATIONAL OBJECTIVES

1. Identify commonly observed sleep abnormalities in patients with Prader-Willi Syndrome (PWS).
2. Discuss the effects of growth-hormone therapy on sleep-disordered breathing in patients with PWS.
3. Identify other sleep-related abnormalities encountered in patients with PWS.

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Disclosure: The authors have no relevant financial relationships to disclose.

doi: 10.3928/00904481-20130924-10

Prader-Willi syndrome (PWS), a complex genetic disorder, is caused by the absence of normally active paternally expressed genes from the chromosome 15q11-q13 region. PWS is an imprinted condition with approximately 70% of the cases caused by a de novo deletion in the paternally inherited chromosome 15q11-q13 region, 25% caused by a maternal uniparental disomy of chromosome 15, and the remaining 5% caused by either microdeletions or epimutations of the imprinting center in the 15q11-q13 region (ie, imprinting defects).[1,2]

Features of PWS include poor feeding in infancy often associated with failure to thrive, obesity beginning around age 2 years, hyperphagia, hypotonia, developmental and cognitive delay, behavioral problems, neuroendocrine abnormalities, and sleep abnormalities. The sleep-related breathing disorders include hypoventilation, obstructive sleep apnea (OSA), central sleep apnea (CSA), and an abnormal arousal and ventilatory response to hypercapnia.[3,4] Various endocrinopathies, including growth hormone (GH) deficiency and central adrenal insufficiency, can contribute to sleep-related breathing disorders in patients with PWS, and the obesity and hypotonia that are associated with this syndrome also can worsen sleep-related breathing issues.[4-7] Therefore, there are a number of factors that place these patients at high risk for sleep-disordered breathing.

POLYSOMNOGRAPHIC CHARACTERISTICS

Patients with PWS have a high prevalence of nocturnal hypoxemia, hypoventilation, and a high respiratory disturbance index, especially during rapid eye movement sleep.[3,4] Even compared with controls with a similar level of obesity, patients with PWS spend more time during sleep with a subnormal oxyhemoglobin saturation (see Figure 1) as a result of sleep apnea, resulting in sleep disruption.[8] Sleep apnea has been shown to occur in 38% to 100% of patients with PWS although many studies have shown that the breathing abnormalities during sleep are mild.[3,4,6,7] The peak incidence of CSA is in infancy, whereas the peak incidence of OSA occurs at 3 to 6 years, which is similar to the general population.[4,9,10] However, within the general population, the prevalence of OSA is only 1% to 3%. In patients with PWS, as in those in the general population, sleep disruption caused by sleep-disordered breathing can cause behavioral and attention issues during the day; therefore, sleep needs to be evaluated in patients with PWS, and sleep-related breathing disorders need to be treated if present.[11-13]

The cause of sleep apnea in patients with PWS has traditionally been thought to be caused by a combination of pharyngeal narrowing, hypoventilation because of respiratory muscle insufficiency, a disconnect between upper airway patency and nocturnal respiratory needs, and decreased ventilatory and arousal response to hypercapnia. Data indicate that the hormone orexin is abnormal in some patients with PWS, supporting the fact that hypothalamic dysfunction may be another cause of some of the sleep-related breathing issues.[3,14] Additionally, abnormal serotonin levels found in patients with PWS may also contribute to sleep and breathing disorders associated with this syndrome.[15] Respiratory failure during pulmonary or systemic illness is the most common cause of death in patients with PWS, and sleep apnea is thought to be the leading cause of these sudden deaths. Both CSA and OSA events increase during times of illness in patients with this syndrome.[5]

CSA appears to be more common in infants with PWS and in people with central adrenal insufficiency. Data have shown that treatment with supplemental oxygen during sleep can help alleviate CSA in infants with PWS, but this treatment needs to be titrated in a sleep laboratory under observation so that hypercarbia or concurrent respiratory events are not worsened.[16] GH treatment can potentially worsen CSA in very young infants with PWS, but it improves CSA in most patients with PWS.[17] CSA in people with central adrenal insufficiency can exacerbate the risk of sudden death caused by illness, so these conditions need to be identified and treated if present.[5]

OSA is present in a large number of patients with PWS (see Figure 2). This is likely caused by a combination of hypotonia leading to upper airway collapse in patients with anatomically narrow airways. Adenotonsillar hypertrophy is thought to be a leading cause of OSA in children with PWS, similar to the general population. Because high levels of GH, such as those observed in people with acromegaly, result in adenotonsillar hyperplasia, it is thought that GH treatment in children with PWS may be a cause of the increased prevalence of OSA.[18] Adenotonsillar hypertrophy narrows the nasopharynx and oropharynx, which leads to obstruction of the upper airway. Studies evaluating the efficacy of tonsillectomy/adenoidectomy in patients with PWS have shown mixed results. One study showed a significant improvement in overall sleep-disordered breathing (based on the apnea-hypopnea index).[19] However, there were many postoperative complications noted in this study. Another small study found that some subjects had an improvement in their apnea-hypopnea index after tonsillectomy/adenoidectomy, but some had minimal or no improvement after the surgery, suggesting that other factors likely play a significant role in OSA in this population.[20] OSA has been found to be significantly correlated with the body mass index z score in children with PWS, as in the general population.

EFFECT OF GH ON POLYSOMNOGRAPHY

In 2000, GH therapy was approved by the US Food and Drug Administration for the treatment of growth failure in children with PWS. Many endocrinologists began using GH off-label in infants and children with a diagnosis of PWS even without evidence of growth failure. In 2003, there were reports of sudden deaths in patients with PWS soon after beginning treatment with GH, prompting a safety warning being issued from GH manufacturers.[21,22] Possible theories as to the relationship of the initiation of GH treatment to the increased sudden deaths included the following: 1) GH treatment alone increased tonsillar/adenoid tissue hypertrophy leading to fatal OSA; 2) a combination of the initiation of GH treatment resulting in increased tonsil/adenoid size with a concurrent upper respiratory infection caused acute occlusion of the airway leading to fatal OSA; and 3) GH caused an increased oxygen requirement because of an increased metabolic rate.[23] Since that time, there have been several studies that show that, overall, GH treatment does not increase the risk of sudden death in patients with PWS.[9,20,24] Additionally, studies have shown that GH treatment does not change the prevalence or severity of OSA.[25] GH therapy improves arterial oxygenation and cardiovascular function during sleep in patients with PWS.[26] Treatment with GH improves the response to carbon dioxide and increases ventilatory output and central inspiratory drive during sleep in patients with PWS.

However, several studies have found that concomitant upper respiratory infections during the initiation phase of GH therapy can cause acute hypoxemia and OSA in young children with PWS, particularly infants.[4] Many studies have shown that the majority of sudden deaths after GH treatment initiation occur during the first 9 months of treatment, so this may be a vulnerable time for children during GH treatment, especially if they develop an upper respiratory infection.[4,27] Some pulmonologists advocate monitoring with several nights of pulse oximetry during the initiation of GH therapy or during upper respiratory infections to determine if there is any evidence of OSA. If there are significant desaturations on pulse oximetry monitoring, then a formal sleep study needs to be performed to quantitate the amount and type of sleep apnea. Some physicians recommend simply that GH treatment be interrupted during times of upper respiratory infections, but there is no evidence to suggest that this is actually beneficial.

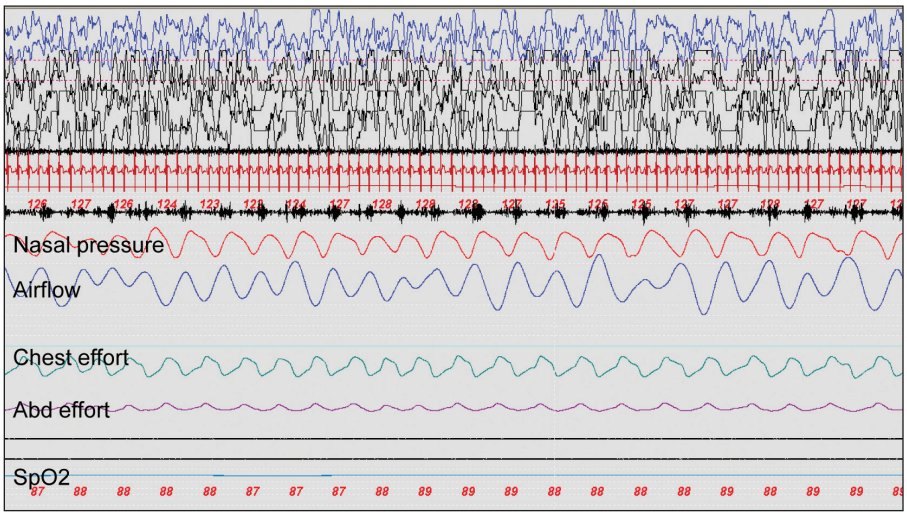

Figure 1. Hypoxemia during sleep in a child with Prader-Willi Syndrome.

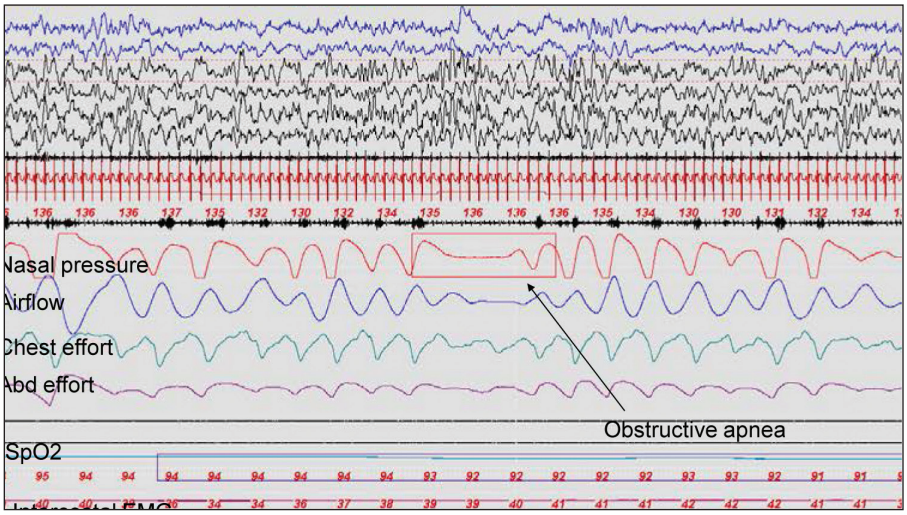

Figure 2. Obstructive sleep apnea in a child with Prader-Willi Syndrome.

Overall, physicians need to be aware that the first 9 months of GH therapy are a vulnerable time for children with PWS, particularly infants and those who have upper respiratory infections. However, the benefits of GH therapy far outweigh the risks of worsening sleep apnea in this population because most studies have found either improvement or no change in the prevalence or severity of OSA with GH treatment.

EXCESSIVE DAYTIME SLEEPINESS (EDS)

EDS is extremely common in patients with PWS. Many patients with PWS have disrupted sleep because of night-

time awakenings or OSA, but EDS does not seem to be necessarily associated with these sleep issues. EDS is thought to be primarily caused by hypothalamic dysfunction, resulting in decreased levels of hypocretin/orexin.[28] Hypocretin is a neurotransmitter in the dorsolateral hypothalamus that regulates sleep, appetite, and metabolism. The degeneration of neurons that contain hypocretin has been shown to be associated with narcolepsy, hypophagia, and obesity.[29] A few studies have shown lower levels of orexin in the cerebral spinal fluid of patients with PWS and EDS.[14,30]

EDS is more common in those patients with a higher body mass index, but otherwise there is no association of EDS with the type of PWS, GH status, or age.[7] In adults with PWS, EDS is the most common type of sleep complaint. EDS is a significant problem for patients with PWS because it has been shown to be associated with severe disruptive behavior and difficulties with attention and learning.[11,31] Certain situations, such as riding in a car or having no engaging activities, seem to provoke EDS in patients with PWS.

One finding that may contribute to EDS in patients with PWS that has not been adequately studied is the frequency of early morning awakening. A majority of parents report that their child with PWS will awaken extremely early in the morning without any apparent cause. In our experience, these children are typically not searching for food when they awaken but will play or read until others awaken. Because typical overnight sleep studies end early in the morning, this phenomenon, which is extremely concerning and disturbing to parents, is typically missed during these studies. Actigraphy could be of benefit in this population to help determine pattern the early morning awakening in addition to parental observation and sleep diaries.

Modafinil, which is a central stimulant, has been reported to be effective in the treatment of EDS in patients with PWS.[32] Further studies need to be performed on this medication to obtain additional data about its effects on behavior, cognitive function, attention, and nighttime sleep patterns in patients with PWS.

NARCOLEPSY

Many patients with PWS have clinical symptoms of narcolepsy including daytime sleepiness, disturbed nocturnal sleep, and cataplexy. Interestingly, in our clinical experience, cataplexy is most often noted in young children with PWS during times of eating, especially right before or after sleep. Multiple sleep latency testing (MSLT) results have been published for a small number of patients with PWS and EDS. These results show that a subset of those with PWS have sleep-onset REM periods during MSLT testing, which is characteristic of narcolepsy, whereas others simply have decreased sleep latency consistent with EDS but not true narcolepsy.[33,34] This is an area that needs additional exploration in patients with PWS to determine the true prevalence of the condition in this syndrome and the best treatments for people with narcolepsy, both with and without cataplexy.

CONCLUSION

Sleep disturbances are common in patients with PWS. Both nocturnal sleep disturbances and daytime sleepiness are significant issues in this population. Interventions including tonsillectomy/adenoidectomy, good weight control, continuous positive airway pressure and bilevel positive airway pressure, and possibly stimulant medications such as modafinil are often necessary in this population. Despite concerns about the effects of GH treatment on OSA, GH therapy does not seem to worsen sleep-disordered breathing in this population. Sleep studies and MSLT testing are extremely beneficial to determine the presence of sleep-disordered breathing or narcolepsy and the possible treatments and effects of treatments in this unique population. ■

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