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How to Understand Sleep and Sleep Problems in Patients with Prader-Willi Syndrome?

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Sleep problems occur frequently among patients with Prader-Willi syndrome (PWS). The most common problem is excessive daytime sleepiness (EDS) that are closely related to of sleep-related breathing disorder (SRBD) such as obstructive sleep apnea (OSA) and congenital hypoventilation syndrome. Obesity, craniofacial dysmorphism and muscular hypotonia of patients with PWS may increase the risk of SRBD. Sleep apneas can interrupt the continuity of sleep, and these disruptions result in a decrease in both the quality and quantity of sleep. In addition to SRBD, other sleep disorders have been reported, such as hypersomnia, a primary abnormality of the rapid eye movement (REM) sleep and narcolepsy traits at sleep onset REM sleep. Patients with PWS have intrinsic abnormalities of sleep-wake cycles due to hypothalamic dysfunction. The treatment of EDS and other sleep disorders in PWS are similar to standard treatments. Correction of sleep hygiene such as sufficient amount of sleep, maintenance of regular sleep-wake rhythm, and planned naps are important. After comprehensive evaluation of sleep disturbances, CPAP or surgery should be recommended for treatment of SRBD. Remaining EDS or narcolepsy-like syndrome are controlled by stimulant medication. Bright light therapy might be beneficial for disturbed circadian sleep-wake rhythm caused by hypothalamic dysfunction.

Keywords: Sleep, Excessive daytime sleepiness, Sleep-related breathing disorder, REM sleep abnormalities, Hypothalamic dysfunction

Introduction

Prader-Willi syndrome (PWS) is a genetic disorder in which hypotonia is the predominant feature in infancy, whereas developmental delay, obesity and behavioral problems become more prominent during childhood and adolescence[1]. Sleep problems occur frequently among individuals with PWS. Because of the development of obesity, craniofacial dysmorphism and muscular hypotonia, patients with PWS are at a risk of sleep-related breathing disorder (SRBD) such as obstructive sleep apnea (OSA) and congenital hypoventilation syndrome[2]. The most common problem is excessive daytime sleepiness (EDS). Sleep disturbances and sleep apnea were initially listed as a minor diagnostic criterion in the diagnosis of PWS[3]. Obstructive sleep apnea is associated with increasing body weight. Sleep apnea can interrupt the continuity of sleep, and these disruptions result in a decrease in both the quality and quantity of sleep. EDS can result from this decrease in sleep efficiency. In addition to SRBD, other sleep disorders have also been reported, such as hypersomnia, a primary abnormality of the circadian rhythm of rapid eye movement (REM) sleep and narcoleptic traits at REM sleep onset[4,5]. Patients with patients may also present with primary abnormal ventilatory responses to hypoxia and hypercapnia, which might be exacerbated byobesity[6]. Besides, patients with PWS have intrinsic abnormalities of sleep-wake cycles due to hypothalamic dysfunction. Since EDS has been correlated with the intrusion of REM sleep into wakefulness, individuals with PWS may appear to have narcolepsy-like symptoms. This article will review the literature regarding sleep problems in patients with PWS and will suggest the optimal management to improve their health and behavioral disturbances as well as patients and families' quality of life.

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Excessive Daytime Sleepiness in Patients with PWS

Patients with PWS frequently experience significant EDS. Most common cause of EDS is chronic sleep insufficiency, and the next is nocturnal sleep disturbance mainly related to SRBD. Central nervous system hypersomnia such as narcolepsy or idiopathic hypersomnia are the third most common causes of EDS in both adults and children with PWS. In a sleep questionnaire study, EDS was commonly described in children with PWS[7]. It was reported that 20 out of 30 pediatric PWS patients were given a score by their caregivers of more than10 on the Epworth Sleepiness Scale, indicating significant EDS[8]. Objectively, moderate to severe sleepiness was noted on the MSLT in 11 out of 18 adult PWS patients[9]. This sleepiness seems to be predominantly in inactive and unengaging situations. Dissimilar results have been reported with respect to correlating EDS in PWS with weight. However, it might be certain that the sleepiness experienced by PWS patients is responsible for the behavioral disturbances observed in PWS patients.

Sleep Related Breathing Disorders in Patients with PWS

OSA is the most frequent SRBD reported in PWS. It may be caused by obesity, sticky saliva, kyphoscoliosis, or adenotonsillar hypertrophy in combination with the narrow upper airways in PWS. Hypotonia of the respiratory muscles may also play a role. Recently, it has been demonstrated that non-obese pre-pubertal PWS children have mainly central sleep apnea and only rarely OSAS during thenight[10]. Patients with PWS are at increased risk for sleep-disordered breathing, in particular OSA and hypoventilation, with weight being a prominent risk factor. Arousal and cardiorespiratory responses to rapidly developing hypoxia and hypercapnia are also absent, decreased, and/or delayed in PWS compared with control subjects of similar age, sex, and BMI[11]. These blunted hypoxic and hypercarbic responses in PWS may suggest potential deficiencies in peripheral chemoreceptors or even central respiratory mechanisms in PWS, which may impact on all forms of SRBD[12]. OSA may lead to several complications, such as systemic hypertension, cardiovascular disease, and cor pulmonale. Cor pulmonale plays an important role in the morbidity and mortality of patients with PWS. Rapid eye movement sleep abnormalities and EDS are common in PWS and are considered a primary disorder. However, SRBD may disrupt sleep and induce ESD in PWS. In patients with PWS, OSA is associated with behavioral disturbances, such as autistic-related behavior and impulsiveness[13]. A recent study in young PWS infants found that OSAS was associated with lower mental development[14].

SRBD and Growth Hormone Therapy

Growth hormone (GH) has become an approved treatment in PWS to improve linear growth, lean-to-fat ratio, mobility, behavior, and quality of life in PWS[15]. GH may lead to respiratory failure in PWS patients include an increase in the size of lymphoid and soft tissues in the upper respiratory tract with GH therapy, an increase in metabolic rate with increased oxygen demand and ventilator load, and a normalization of previously decreased hydration, which increases volume load[15]. It is suggested that close attention be made to obesity and sleep and breathing problems both before and after commencement of GH treatment, with a low threshold for ear, nose, and throat assessment and polysomnography.

REM Sleep Abnormalities in Patients with PWS

Several studies have documented the presence of significant REM sleep dysregulation in PWS in the form of shortened REM latency, and increased prevalence of SOREMPs on overnight polysomnography or the multiple sleep latency test (MSLT)[16-18]. Such REM dysregulation implies a disruption in the circadian rhythms of PWS patients or a dysfunction in fundamental sleep-wake mechanisms. We also observed that a shorter sleep latency and REM latency in the PWS group[19]. It suggested that REM sleep abnormalities in children with PWS than normal children. Such REM dysregulation may be linked with the abnormal thermoregulation observed in PWS, pointing to hypothalamic dysfunction as the cause of such dysregulation[5].

Hypothalamic Dysfunction and Narcolepsy-like Syndrome in Patients with PWS

The presence of REM abnormalities and EDS not otherwise explained suggests the presence not only of a narcolepsy-like syndrome in patients with PWS, but narcolepsy itself. The majority of studies, however, have not reported the presence of narcolepsy symptoms in their PWS samples, including cataplexy, hypnagogic/hypnopompic hallucinations, and sleep paralysis[20]. Hypocretin (orexin) is a peptide neurotransmitter found in the dorsal and lateral hypothalamus. Narcolepsy in humans has been associated with decreased hypocretin CSF levels and degeneration of hypocretin neurons. In addition to its role in sleep regulation,

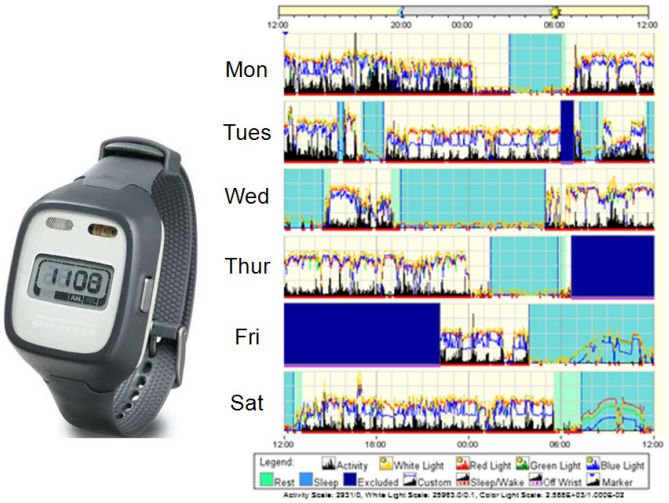

Fig. 1. Actigraphy and actogram of a patient with disturbed sleep-wake pattern. A patient is a 22 year-old college student who suffered from sleep onset insomnia and excessive daytime sleepiness. A week of actogram showed irregular sleep-wake pattern combined with delayed sleep-wake cycles. Data was recorded by Actiwatch Spectrum 2 (Philips, Andover, MA, USA) Blue bars represent sleep time recorded by actigraphy. Dark-blue bar indicate the time of taking off the watch.

hypocretin/orexin has been associated with a number of other effects including appetite regulation, autonomic and endocrine function, and pleasure-reward pathways[21]. Mignot et al.[22] identified a 16-year-old with PWS with low levels (≤110 pg/mL by direct radioimmunoassay) of CSF hypocretin comparable to that of narcolepsy. Based on the limited evidence it seems that the sleepiness in PWS is associated with a deficiency of hypocretin/orexin in the hypothalamus, but not necessarily a degeneration of hypocretin neurons as is seen in narcolepsy.

Disturbed sleep-wake pattern and irregular sleep cycles in PWS are responsible for hypothalamic dysfunction, in particular, suprachiasmatic nucleus located in anterior hypothalamus. It is well-known that bright light therapy with scheduled melatonin administration may normalize disturbed sleep-wake cycle[23]. Circadian abnormalities are monitored with actigraphy[24] (Fig. 1). Actigraphic data were recorded in eight children with the rare genetic condition mucopolysaccharidosis (MPS) type III over 7–10 days and showed impairment in circadian rhythm functioning in children with this condition[25]. Recently, two studies with small numbers of PWS children demonstrated that children with PWS had a shorter sleep latency but more time awake in the night than normal children and have similar total sleep time and morning wake time compared with controls[26,27]. However, disturbed sleep-wake patterns were not evident in those studies. In future, a larger number of study subjects and age-adjusted study protocol would be required to obtain a definite conclusion.

Treatment of Sleep Problems in Patients with PWS

The first intervention is to improve sleep hygiene by shaping behavior to assure the appropriate amount of sleep and to supplement this with planned naps, if necessary. The second intervention is to treat the source of sleep disruption; CPAP is needed for OSA or intermittent hypoxemia. However, cases where the treatment of SRBD in PWS does not alleviate daytime sleepiness[28-32], further reinforce the hypothesis that SRBD alone cannot account for the presence of daytime sleepiness in this population. Then, the daytime use of stimulant medication (methylphenidate) and/or modafinil are recommended. Besides, weight loss and upper airway surgery might be beneficial for sleep problems in PWS[33]. Identification and treatment of sleep problems in patients with PWS would definitely improve physical and mental health as well as quality of life of families[34].

Conclusion

EDS is a frequent and significant symptom of patients with PWS. There are a number of risk factors that predispose them to SRBD, but OSA in itself does not account for all of the EDS experienced by such patients. Hypothalamic dysfunction is implicated in patients with PWS, and such dysfunction likely explain narcolepsy-like syndrome and circadian rhythm sleep-wake disorder observed in PWS patients. It is important for both physician and parents/care providers pay more attention on sleep problems in patients with PWS.

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