Chapter

36 Sleep abnormalities and Prader–Willi syndrome

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Introduction

Prader–Willi syndrome (PWS) is a complex, multisystem genetic disorder with an estimated prevalence of 1/15,000 to 1/30,000. Characteristic features include neonatal hypotonia, short stature, facial dysmorphia, hypogonadism, hyperphagia with morbid obesity, failure of satiety, developmental delay with mild to moderate retardation, and a number of behavioral and psychiatric disturbances (including maladaptive behaviors pertaining to food, temper tantrums, obsessive–compulsive tendencies, and other symptoms consistent with an autism spectrum disorder). This constellation of symptoms is highly suggestive of the presence of hypothalamic dysfunction in such individuals. The genetics of PWS are complex, but in general PWS is the result of an absence of the normally active paternally derived genes in the chromosome 15q11–13 region. In approximately 70% of cases, this is the result of deletion of the paternally derived 15q11–13 region. Approximately 25% of PWS cases are due to maternal disomy of chromosome 15 (two maternal copies of the maternal chromosome 15). The remainder of cases result from translocations involving chromosome 15 or microdeletions of the imprinting center within 15q11–q13 [1–6].

Sleep disturbances, in the form of excessive daytime sleepiness (EDS), and sleep apnea, were initially listed as a minor diagnostic criterion in the diagnosis of PWS, based on earlier case reports [6]. However, in the last two decades the prominence of excessive daytime sleepiness in PWS patients has become increasingly recognized, and a number of investigators have looked at the correlates and potential causes of the sleepiness associated with this condition. This chapter will review this literature, beginning with a review of the prevalence and extent of sleepiness in PWS, the potential contribution of sleep-disordered breathing to this sleepiness, and finally evidence suggesting the presence of a primary hypersomnolence in patients with PWS. What is evident from such a review is that the cause of sleepiness in PWS is not a straightforward matter. While sleepiness in the PWS patient poses particular challenges to the treating physician, it may also provide significant insights into the basic mechanism regulating sleep and wakefulness.

Sleepiness and Prader–Willi syndrome: prevalence, extent, and correlates

In a large survey given to caregivers of adult PWS patients (N = 232), Greenswag [7] found that such patients were commonly rated as being "sleepy." Such sleepiness moreover was correlated with patient weight. In a similar survey (N = 61), Clarke *et al.* [8] found that adult PWS patients were frequently rated as experiencing excessive daytime sleepiness as well as increased nocturnal sleep. Such sleepiness, however, did not seem to correlate with patient weight, nor did it correlate with a number of behavioral abnormalities surveyed. Richdale *et al.* [9] in a survey of 29 pediatric and adult subjects with PWS found the presence of subjective daytime sleepiness in ten subjects, in comparison with no subjects in a control group. The PWS group also scored significantly higher on the Epworth Sleepiness Scale (ESS) than the control group. The authors did not find a correlation between excessive daytime sleepiness and body mass index (BMI) or weight in the PWS group. They did find, in the PWS group, a correlation between daytime sleepiness as measured by the ESS and a number of behavioral disturbances on the Developmental Behaviour Checklist

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(DBC). In a sleep questionnaire study, Cotton and Richdale [10] found excessive daytime sleepiness to be commonly described in children with PWS, but rarely in other intellectual disability groups including autism and Down Syndrome. Hass *et al.* [11] found ratings of sleepiness in a scatter plot analysis of seven PWS adult patients to be more common during periods when there were no scheduled activities, confirming anecdotal reports that PWS patients tend to fall asleep during passive, unengaging activities.

A number of other studies conducted in sleep laboratories have also corroborated the presence of subjective or caregiver reported excessive daytime sleepiness in patients with PWS, although such studies generally involve patients being referred to a sleep laboratory for various reasons and may be prone to selection bias. Vela-Bueno *et al.* [12] reported the presence of symptomatic excessive daytime sleepiness in eight out of nine pediatric and adult patients with PWS referred to their study. Kaplan *et al.* [13] reported the experience of hypersomnolence in all five patients investigated in their study. Clift *et al.* [14] found that 12 out of 17 PWS patients exhibited daytime sleepiness based on either caregiver ratings, the ESS, or the MSLT. Subjective ratings of alertness, on the other hand, were normal. Richards *et al.* [15] found evidence of excessive daytime sleepiness in 8 out of 14 adult PWS patients based on caregiver ratings and on the Epworth Sleepiness Scale (ESS >9). Manni *et al.* [16] reported that all 14 adult and pediatric PWS patients they studied (unselected for sleep disorders) were reported by caregivers as being sleepy during the day. Williams *et al.* [17] reported that 20 out of 30 pediatric PWS patients were given a score by their caregivers of ≥ 10 on the ESS, indicating significant daytime sleepiness.

A number of studies have also looked at the presence of objective sleepiness in patients with PWS, although again, these studies were conducted on patients referred to a sleep clinic and as such are prone to selection bias. Harris *et al.* [18] demonstrated moderate to severe sleepiness in four out of four PWS patients, two with what would be considered severe or pathological sleepiness (mean sleep latency <5 minutes) with each patient exhibiting one SOREM nap. Hertz *et al.* [19] conducted MSLTs on fourteen adult patients with PWS and found that ten patients exhibited daytime sleepiness on MSLT testing (MSLT <10 minutes), with six exhibiting severe sleepiness (mean sleep latency <5 minutes). Helbing-Zwanenburg *et al.* [20] found evidence of excessive daytime sleepiness in 20 out of 21 randomly chosen adult PWS patients (95%) based on 24-hour ambulatory recording, in comparison to 2 out of 19 controls (10%). Clift *et al.* [14] found 7 out of 14 PWS patients exhibited pathological sleepiness on the MSLT. Richards *et al.* [15] reported pathological sleepiness on the MSLT in four out of ten patients. Vgontzas *et al.* [21] reported moderate to severe sleepiness in five out of eight PWS subjects based on a modified MSLT protocol. Hiroe *et al.* [22] reported moderate to severe sleepiness in all three PWS cases they subjected to the MSLT. Manni *et al.* [16] reported abnormal MSLT values in eight out of ten PWS subjects they investigated (even taking into account Tanner staging for adolescent patients). Priano *et al.* [23] reported moderate to severe sleepiness on the MSLT in 11 out of 18 adult PWS patients studied. Williams *et al.* [17] reported a mean MSLT of nine minutes in 20 pediatric PWS patients with five patients exhibiting an MSLT score consistent with narcolepsy, with two SOREMP and an average mean sleep latency in this subgroup of 5.9 minutes.

In summary, patients with PWS frequently experience significant excessive daytime sleepiness, based on subjective and objective criteria such as the MSLT. This sleepiness seems to be predominantly in passive, unengaging situations, but there is a paucity of data with respect to characterizing alertness in such patients, including performance on the Maintenance of Wakefulness Test (MWT). Mixed results have been found with respect to correlating excessive daytime sleepiness in PWS with weight. Finally, some studies have suggested that the sleepiness experienced by PWS patients may account for some of the behavioral disturbances observed in such patients, arguing for the effective assessment and management of such sleepiness in the overall care of PWS patients.

Sleep-disordered breathing and Prader–Willi syndrome

One obvious explanation for the presence of sleepiness in patients with PWS would be sleep-related breathing disorders, which patients with PWS may be at risk for. Specifically, this population may be at risk for the development of obstructive sleep apnea/hypopnea syndrome because of obesity, hypotonia, viscous secretions, cranio-facial dysmorphism, and alveolar hypoventilation due to an increased presence of restrictive lung disease and absent or reduced

ventilator responses to hypercapnia and hypoxia [24]. As a result, a number of studies have investigated the presence and nature of sleep-disordered breathing in PWS.

Prevalence of sleep disordered breathing in Prader–Willi syndrome

A number of studies have indeed confirmed the presence of sleep-disordered breathing in PWS, whether in the form of sleep apnea or hypoventilation. Freidman *et al.* [25] found significant sleep apnea in four out of nine pediatric and adult patients with PWS, while another two exhibited prominent oxygen desaturations in sleep in the absence of apneic events, and another two exhibited mild central apnea. Harris *et al.* [18] reported significant apneas and REM related hypoxia in three out of four PWS patients. Clift *et al.* [14] found that 16 out of 24 PWS patients exhibited significant REM-related oxygen desaturations in REM sleep. Seven patients were deemed to have significant sleep apnea with desaturations worthy of treatment with continuous positive airway pressure (CPAP). Richards *et al.* [15] found significant sleep apnea (AHI $>$ 10) in 12 of 14 adult PWS patients.

O'Donaghue *et al.* [26] found significant sleep apnea (AHI $>$ 10/hour) in 9 of 13 (69%) "unselected" PWS subjects. Four subjects also exhibited pathological rises in $TcCO_2$ ($>$10 mm Hg) with two meeting the criteria for obesity hypoventilation syndrome. Furthermore, they demonstrated that increased age-adjusted BMIs were associated with more severe hypoxia (minimum SaO_2) during the night and more sleep disturbances (high arousal index and low sleep efficiency). Subjective daytime inactivity/sleepiness was associated with higher AHIs, lower minimum SaO_2, and higher BMIs. They also found that higher impulsivity was associated with lower minimum SaO_2, an increased arousal index and higher BMIs.

Priano *et al.* [23] found significant sleep apnea (AHI $\geq$ 5) in 6 out of 22 PWS patients studied, although 15 patients in their study had prolonged periods of oxygen desaturation, commonly in REM sleep.

Festen *et al.* [27] found a median AHI of 5.1 in 53 pediatric patients with PWS participating in a randomized controlled trial of growth hormone. Most of the events, however, were central in nature. No correlation was found between AHI and BMI. However, the authors also reported that 4 out of 45 (9%) non-obese patients exhibited obstructive sleep apnea as defined by an obstructive apnea index $>$1, while 4 out of 8 (50%) obese patients did likewise. In a subgroup of these patients (n = 35) a follow-up PSG, done after six months of growth hormone (GH) treatment, resulted in a non-significant decline in the AHI.

Yee *et al.* [28] found significant sleep apnea (defined as a Respiratory Disturbance Index (RDI) $>$5 events/hour) in 18 out of 19 (95%) PWS patients referred consecutively from a PWS clinic. The mean total RDI for the PWS group, however, was not significantly different from an obese control group, although the PWS group exhibited more significant nocturnal hypoxia. Nine of the PWS patients also fulfilled the criteria for obesity hypoventilation syndrome, based on BMI and arterial blood gases.

Lin *et al.* [29] found a mean RDI of 5.8 $\pm$ 3.7/hr in a group of 30 PWS subjects (not selected for complaints of sleep problems). A roughly equal proportion of central and obstructive apneas were observed. An RDI of $>$2 was observed in 28 out of 30 (93%) subjects and an RDI of $>$10 in 5 subjects (17%). The authors also noted a desaturation index (DI) (desaturations $>$4%) of 8.1 $\pm$ in the group. Age-adjusted BMIs were associated with more severe hypoxemia in sleep (based on a number of measures) and more sleep disturbance (based on the arousal index). The authors did not find a correlation between any sleep variable and genotype.

Festen *et al.* [30] found evidence of sleep-disordered breathing in 22 PWS infants entered into their study, with a median AHI of 6.1 events per hour, with the majority of events recorded being central in nature. Overall AHI did not correlate with psychomotor development as measured by the Bayley Scales of Infant Development – II, although four infants who had obstructive sleep apnea syndrome exhibited more severely delayed mental development.

Williams *et al.* [17] reported that in a retrospective review of 37 pediatric patients referred to their clinic with suspected sleep disordered breathing, 70% demonstrated an elevated AHI ($\geq$1/hour), 86% showed significant hypoxemia (oxygen desaturation $<$93%), and 62% having significant hypercarbia (end tidal $CO_2 > 50$ mmHg). All 37 patients demonstrated significant sleep-disordered breathing in one of these three forms. The authors found a positive correlation between AHI and adjusted BMI. A similar association between BMI and AHI, as well as measures of oxygen desaturation, were described by Hertz *et al.* [31].

On the other hand a number of studies have failed to demonstrate the expected increased prevalence of sleep-disordered breathing in PWS. In an early study, Vela-Bueno *et al.* [12] studied nine pediatric and adult patients with PWS with two to four consecutive overnight studies. Despite the fact that all the patients complained of excessive daytime sleepiness, only one exhibited the presence of obstructive sleep apnea. One patient was noted to have severe hypoventilation in REM sleep.

Kaplan *et al.* [13] reported a mildly elevated AHI in only one of five pediatric and adult PWS patients studied, despite all five patients experiencing daytime hypersomnolence and having morbid obesity. Two patients in their sample exhibited significant oxygen desaturations attributed to hypoventilation in REM or NREM sleep. Helbing-Zwanenburg *et al.* [20] did not find significant sleep apnea in any of 13 cases investigated for this. Hertz *et al.* [19] investigated 24 adult and pediatric patients for sleep apnea. Despite a high prevalence of morbid obesity and MSLT-confirmed daytime sleepiness in the sample, only three patients exhibited significant sleep apnea (AHI $>$ 10/hour). Nine patients in their sample exhibited significant nocturnal oxygen desaturations, generally during REM sleep. Moreover basal SaO_2 and lowest SaO_2 correlated with BMI. The authors noted that nocturnal desaturation and AHI correlated with daytime sleepiness as measured by the MSLT, although a number of patients exhibited significant daytime sleepiness in the absence of sleep-disordered breathing. Vgontzas *et al.* [21] did not find significant sleep-disordered breathing or hypoventilation in any of eight PWS subjects studied. Hiroe *et al.* [22] found mild sleep apnea syndrome in only one of three PWS cases studied (employing esophageal monometry), despite the presence of daytime sleepiness based on the MSLT in all three cases. Manni *et al.* [16] found an elevated respiratory distress index (RDI) in four out of fourteen PWS subjects, with three exhibiting significant oxygen desaturations during the night, despite the presence of daytime sleepiness in all subjects. Voloh *et al.* [32] found significant sleep apnea in only 1 of 14 pediatric and adult PWS patients studied.

As discussed by Nixon and Brouillette [24], studies on the presence of sleep-disordered breathing in PWS (including sleep apnea and hypoventilation) have given prevalence estimates in the range of 0 to 100%, with the most obvious influencing factor being variable inclusion criteria used in such studies. Other potential criticisms of such studies include small sample sizes, mixed pediatric and adult sample groups, and variable methods for recording and defining respiratory events (including the use of adult criteria for pediatric patients).

Overall, however, it does seem reasonable to conclude that patients with PWS are at increased risk for sleep-disordered breathing, in particular obstructive sleep apnea and hypoventilation, with weight being a prominent risk factor. However, it is also apparent that sleep-disordered breathing alone cannot fully account for the sleepiness experienced by patients with PWS. At both the individual and group level we see patients with PWS and significant daytime sleepiness who do not have any sleep-disordered breathing, or in whom sleep-disordered breathing is disproportionate to the degree of daytime sleepiness present.

Prader–Willi syndrome and abnormal ventilatory response

A number of studies have suggested that there may be more to sleep-disordered breathing in Prader–Willi syndrome than obstructive phenomena. As noted, several studies have documented an increased prevalence of central events in PWS [27, 29, 33]. Several studies have also demonstrated that PWS patients have abnormal ventilatory control during wakefulness, including abnormal ventilatory responses to hyperoxia, hypoxia, and hypercarbia [34–36]. A number of studies have also demonstrated abnormalities in ventilatory control during sleep. Livingston *et al.* [37] found a significantly elevated central apnea index (1.5 ± 0.4/hour) in ten PWS patients studied, in comparison with nine controls (0.1 ± 0.1/hour), in addition to a significantly higher baseline and peak end tidal CO_2 levels. Moreover the authors found that the PWS group exhibited a significantly higher arousal threshold in response to a hypercapnic challenge during slow-wave sleep. No differences were found between the groups in terms of obstructive events or hypoxemia. Arens *et al.* [38] reported a decreased arousal and cardiorespiratory response to a hypoxic challenge during slow-wave sleep in 13 adult PWS patients. Schlüter *et al.* [39] investigated eight pediatric PWS patients (including infants) in comparison with matched controls. The PWS group did not exhibit an increased incidence of obstructive apneas but did exhibit an increased number of all apneas $>$2 seconds duration per hour of sleep, as well as decreased nadir of oxygen desaturation and decreased respiratory response to hypercapnia.

In summary several studies have documented blunted hypoxic and hypercarbic responses in PWS, suggesting potential deficiencies in peripheral chemoreceptors or even central respiratory mechanisms in PWS (see below regarding the relevance of this to the use of growth hormone treatment in PWS), which may impact on all forms of sleep-disordered breathing.

Treatment of sleep-disordered breathing and PWS

Few studies have looked at the treatment of sleep apnea in PWS, but those studies that have reported such treatment provide further insights into the presence of sleep apnea in PWS, and its relationship to excessive daytime sleepiness in such patients. Friedman *et al.* [25] reported one PWS patient with obstructive sleep apnea undergoing tonsillectomy and adenoidectomy with his symptoms improving "somewhat." Harris *et al.* [18] reported a dramatic improvement in sleep apnea in one PWS patient with weight loss, improvement on the MSLT, but persistent daytime sleepiness. In another study, Harris *et al.* [40] also reported persistent daytime sleepiness in a group of PWS patients despite a resolution of their sleep-disordered breathing following weight loss. Sforaza *et al.* [41] reported the case of a 20-year-old patient with moderate sleep apnea successfully treated with CPAP. Hertz *et al.* [19] reported two pediatric patients who experienced significant improvement in their sleep apnea with tonsillectomy and adenoidectomy. Hiroe *et al.* [22] reported continued sleepiness in a 15-year-old boy with PWS, despite resolution of his mild sleep apnea with a uvulopalatopharyngoplasty (UPPP). This case emphasizes that there may be more than one cause of EDS in patients with PWS and treatment of sleep apnea may be necessary but not sufficient to remove EDS in PWS. Pavone *et al.* [42] demonstrated a significant improvement in both the median AHI and median oxygen desaturation index (ODI) in five pediatric PWS patients undergoing adenotonsillectomy. Clift *et al.* [14] treated seven PWS patients with CPAP, with most respiratory events being abolished. Of the five patients who were compliant with treatment over six months, three experienced an improvement in daytime sleepiness. Vgontzas *et al.* [43] reported a case of severe obstructive sleep apnea in a 21-year-old female with PWS, which was successfully treated with CPAP, but with continued sleepiness as exhibited by the MSLT. A repeat study after significant weight loss revealed an absence of sleep apnea, but with persistent sleepiness and REM abnormalities on daytime napping. Esnault-Lavandier and Mabin [44] employed clomipramine (20 mg/day) in the treatment of an 11-year-old boy with PWS, with elimination of his excessive daytime sleepiness, as measured by the MSLT, despite persistence of severe obstructive sleep apnea syndrome.

In summary, treatments proposed for the sleep-disordered breathing associated with PWS run the full range of treatment options available to non-PWS patients, and include surgery, CPAP, and conservative measures such as weight loss. Such treatments do seem to be generally successful in alleviating sleep-disordered breathing in PWS patients. However, cases where the treatment of sleep-disordered breathing in PWS does not alleviate daytime sleepiness [14, 18, 22, 25, 40, 43] further reinforce the hypothesis that sleep-disordered breathing alone cannot account for the presence of daytime sleepiness in this population.

Sleep-disordered breathing: Prader–Willi syndrome and growth hormone therapy

In the last decade, growth hormone (GH) has become an approved treatment in PWS, having been shown to improve linear growth, lean-to-fat ratio, mobility, behavior, and quality of life in PWS [45]. However, concerns have been raised with regards to the use of GH in PWS following a number of case reports detailing sudden death in PWS shortly after the initiation of GH treatment. A number of the reported cases involved respiratory failure, and included cases associated with sleep-disordered breathing [45, 46]. Mechanisms by which 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 [45].

Beyond case descriptions, studies to date have failed to definitively demonstrate an exacerbation of sleep-disordered breathing with GH, and some have even shown an improvement in respiratory function. In a double-blind, placebo-controlled cross-over study in 12 PWS patients, Haqq *et al.* [47] found a significant improvement in a number of pulmonary function measures (peak flow, percentage vital capacity, forced expiratory rate) after six months of GH treatment. Moreover, GH treatment was associated with a

decrease in the number of apneas and hypopneas exhibited by patients on polysomnography, although this decrease was not statistically significant. Festen *et al.* [27] found a non-significant decrease in the AHI in 35 PWS patients after six months of GH treatment. Williams *et al.* [17] did not find a significant difference between measures of sleep-disordered breathing in 16 PWS patients on GH treatment and those not on such treatment. Miller *et al.* [48] examined 25 PWS patients both before and after six weeks of GH treatment. Growth hormone treatment was associated with a reduction in the AHI in 19 patients (in particular with regards to central events) but a worsening in 6 patients. The authors hypothesized that a sub-group of PWS patients may be at risk for a worsening of sleep-disordered breathing with GH treatment. Lindgren *et al.* [49] demonstrated improved resting ventilation, central inspiratory drive, and ventilator response to CO_2 during wakefulness in nine PWS patients after six to nine months of GH treatment.

Given the ongoing concerns around GH treatment and sleep-disordered breathing, it has been recommended that all children with PWS for whom GH is being proposed undergo overnight polysomnography as well as an otorhinolaryngologic examination, and that any sleep-disordered breathing identified be aggressively treated prior to initiating GH therapy [45, 46]. One group has also recommended repeat polysomnography after six weeks of GH therapy [48].

Summary

Patients with Prader–Willi syndrome do seem to have a higher prevalence of sleep-disordered breathing, in the form of obstructive sleep apnea or hypoventilation, with weight being a prominent risk factor. Moreover an increased prevalence of central events and blunted hypoxic and hypercarbic responses suggest the presence of deficiencies in peripheral chemoreceptors or central respiratory mechanisms in PWS patients, which may further contribute to the sleep-disordered breathing in this population. However, it is also apparent that sleep-disordered breathing alone does not fully account for the presence of excessive daytime sleepiness in PWS patients. Patients with PWS have exhibited an absence of sleep-disordered breathing, or a level of sleep-disordered breathing disproportionate to the degree of daytime sleepiness present. Moreover the treatment of sleep-disordered breathing in this population does not necessarily lead to a complete alleviation of sleep-disordered breathing. Clearly the excessive sleepiness in this population is multifactorial in origin with sleep-disordered breathing representing only one contributory factor.

The above considerations aside, sleep-disordered breathing in PWS has been show in many cases to be a significant contributor to the daytime sleepiness associated with PWS patients and has been associated with an increased risk of death in such patients, both with and without GH therapy [45]. Sleep-disordered breathing may also contribute to the cognitive and behavioral deficits in PWS patients, as it does in the non-PWS population [50]. As such, clinicians should have a high suspicion of sleep-disordered breathing in patients with PWS and a low threshold for proceeding with appropriate investigations (including polysomnography). Treatment options, based on case reports, include the full range of typical treatments for sleep-disordered breathing in non-PWS patients with sleep-disordered breathing, and include weight loss, CPAP therapy, and surgery.

Primary hypersomnolence and Prader–Willi syndrome

As noted above, a number of studies looking at the presence of sleep-disordered breathing in PWS have led to the general consensus that the sleep-disordered breathing alone cannot account for the significant excessive daytime sleepiness experienced by PWS patients. This fact, in addition to an absence of any other identifiable sleep disorders, has led to the conclusion that the sleepiness of PWS may also be due to a primary, idiopathic or "narcolepsy-like" sleepiness, with hypothalamic dysfunction playing a putative role. The evidence for this comes primarily from the presence of REM abnormalities in PWS patients, and more recently studies on hypocretin/orexin.

REM sleep abnormalities and Prader–Willi syndrome

Vela-Bueno *et al.* [12] were the first to note an increased prevalence of REM abnormalities in PWS. In their study of nine pediatric and adult patients with PWS, five were noted to have a SOREM in at least one of two to four overnight sleep studies. These REM abnormalities were notably in the absence of significant obstructive sleep apnea. Harris *et al.* [18]

reported moderately shortened REM latencies in two out of four PWS patient during overnight polysomnography with all four patients exhibiting one SOREM nap on MSLT testing, although three of these patients exhibited significant sleep apnea. Kaplan *et al.* [13] noted normal sleep architecture and REM onset latency in the overnight polysomnography of five patients studied. Helbing-Zwanenburg *et al.* [20] noted SOREM episodes in the overnight studies of 7 out of 21 PWS patients studied, with 7 PWS patients also exhibiting SOREM episodes during daytime naps (vs. none in a control group). Hertz *et al.* [19] found that 13 out of 24 adult and pediatric PWS patients exhibited shortened REM latency on polysomnography. Five patients exhibited at least one SOREM episode on the MSLT. Rapid eye movement parameters did not correlate with nocturnal oxygen desaturation nor daytime sleepiness as measured by the MSLT. Clift *et al.* [14] found normal REM latency without any clear SOREM episodes in 17 pediatric and adult PWS patients. Livington *et al.* [37] reported sleep onset REM during overnight polysomnography in seven out of ten PWS patients studied. Vgontzas *et al.* [21] reported three out of eight subjects having shortened REM latency on overnight polysomnography, and four subjects experiencing at least one SOREM episode during two daytime naps. Prader–Willi syndrome patients with EDS also had a higher number of REM periods and shorter REM intervals in comparison with their non-EDS counterparts, as well as normal, narcoleptic, and obese control groups. Manni *et al.* [16] found REM sleep onset in three out of fourteen PWS subjects during overnight polysomnography, and five out of ten subjects experiencing at least two SOREMPs on the MSLT. Yee *et al.* [28] found the mean REM latency during overnight polysomnography to be significantly shorter in a group of 19 adult PWS patients in comparison to an obese control group, despite comparable mean total RDI scores (although the PWS group did exhibit significantly more nocturnal hypoxemia). Lin *et al.* [29] found a shortened mean REM latency of 67.4 ± 30 minutes in a group of 30 pediatric PWS patients. Williams *et al.* [17] reported a normal mean REM latency in 37 pediatric PWS patients of 84 ± 57 minutes, although the large variability in this result is notable.

Sforza [41] reported a case of a 20-year-old patient with PWS with a SOREMP on overnight polysomnography and SOREMP on four out of six naps on a modified MSLT, in addition to moderate sleep apnea. Treatment with CPAP resulted in elimination of sleep apnea, but with a persistent SOREMP on the first night of treatment. Vgontzas *et al.* [43] reported a patient with persistent shortened REM latency and SOREM episodes on daytime sleepiness following successful treatment of severe sleep apnea with weight loss.

In summary, a number of 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 MSLT. In general this REM dysregulation does not seem to be accounted for by the increased prevalence of sleep-disordered breathing in this population, nor any other obvious sleep disorders. Such REM dysregulation implies a disruption in the circadian rhythms of PWS patients or a dysfunction in fundamental sleep–wake mechanisms (or both). These observations also suggest the presence of a primary hypersomnolence akin to narcolepsy, which is itself associated with excessive daytime sleepiness and REM sleep dysregulation. Finally such REM dysregulation may be linked with the abnormal thermoregulation observed in PWS, pointing to hypothalamic dysfunction as the cause of such dysregulation [12]. This in turn has some implications with respect to treatment strategies for PWS patients (see below).

Prader–Willi syndrome and narcolepsy

The presence of REM abnormalities and excessive daytime sleepiness not otherwise explained suggests the presence not only of a narcolepsy-like syndrome in patients with Prader–Willi syndrome, 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. Some exceptions include Helbing-Zwanenburg *et al.* [20], who reported that the presence of cataplexy in 6 of 21 patients with PWS and EDS was "very likely," but commented that cataplexy was even more difficult to prove in the PWS population than in narcolepsy. Clift *et al.* [14] described three out of 17 PWS patients with a loss of muscle tone triggered by laughter, but felt that this was unlikely to be true cataplexy with REM sleep atonia, but rather an exaggerated physiological response in patients with pre-existing hypotonia. A number of small studies conducting HLA bloodtyping in PWS patients have not found a pattern

consistent with a narcoleptic population [16, 19, 20]. Vgontzas *et al.* [21] reported significant differences in the sleep and REM patterns of a PWS group in comparison with a group of patients with narcolepsy. They hypothesized that PWS was associated with a "generalized hypoarousal" with REM abnormalities appearing as a compensatory mechanism.

Overall, while the hypersomnolence associated with PWS appears to be primary in nature and associated with dysregulation of REM sleep, features shared by the condition known as narcolepsy, it does not seem to be due to narcolepsy itself. However, the presence of cataplexy in some patients suggests an increased prevalence of narcolepsy in the PWS population. Alternatively, the putative role of the hypothalamus in both narcolepsy (see below) and PWS point to overlapping pathophysiological mechanisms, and hence shared symptomology. Of note another primary hypersomnia, which is hypothesized to involve hypothalamic involvement, is Klein–Levin syndrome, and at least two cases with both PWS and Klein–Levin syndrome have been reported [51, 52].

Hypocretin/orexin and Prader–Willi syndrome

Hypocretin (known synonymously as orexin) is a peptide neurotransmitter found in the dorsal and lateral hypothalamus. Soon after its discovery, disturbances in the hypocretin system were identified as playing a pathophysiological role in narcolepsy. Narcolepsy in humans has been associated with decreased hypocretin CSF levels and degeneration of hypocretin neurons. In addition to its role in sleep regulation, hypocretin/orexin has been associated with a number of other effects including appetite regulation, autonomic and endocrine function, and pleasure/reward pathways [53].

In keeping with the proposed role of hypothalamic dysfunction in the etiology of the primary hypersomnolence associated with PWS, a number of studies have reported decreased CSF hypocretin levels in patients with PWS. In a large study of CSF hypocretin-1 levels in patients with hypersomnolence, Mignot *et al.* [54] identified a 16-year-old with PWS with low levels ($\leq$110 pg/ml by direct radioimmunoassay) of CSF hypocretin comparable to that of narcolepsy. In a similar study in children with a variety of neurological disorders, Arri *et al.* [55] identified a neonate with PWS with intermediate ($\geq$110 to $\leq$200 pg/ml) levels of CSF hypocretin-1. Dauvilliers *et al.* [52] reported the case of a 21-year-old male with both PWS and Klein–Levin syndrome who exhibited a nearly twofold decrease in CSF hypocretin-1 during an episode of hypersomnia (111 pg/ml) in comparison with levels taken when asymptomatic (221 pg/ml). Nevsimalova *et al.* [56] reported the findings of low and intermediate levels of CSF hypocretin-1 in two cases of PWS, who exhibited severe and moderate levels of daytime sleepiness on the MSLT respectively. Another two cases, without daytime sleepiness, exhibited normal CSF hypocretin-1 levels.

Finally, Fronczek *et al.* [57] studied the postmortem hypothalami of seven PWS patients and found no significant difference in the number of hypocretin neurons between the PWS group and a group of controls.

Overall, the findings noted above, albeit limited, support the notion of hypothalamic dysfunction as the cause of excessive daytime sleepiness seen in PWS syndrome. 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.

Treatment of primary sleepiness in Prader–Willi syndrome

Treatment of the primary sleepiness in PWS has been severely limited. Behavioral measures, such as extended nocturnal sleep, have been proposed. A limited number of case reports have reported a beneficial impact of stimulants in the excessive daytime sleepiness associated with PWS, but concerns have been raised about the adverse effects such medications can have on appetite and behavior [24]. One potentially beneficial, but as yet untested, treatment for primary sleepiness associated with PWS is the wakefulness agent modafinil [58]. We have used the amino acid tryptophan in doses up to 4.5 g in children and adults with PWS showing hypersomnolence. This has usually been in the context of showing fragmented sleep in polysomnographic recordings. We have had dramatic resolution of hypersomnia in some patients and, in a couple of cases, we have had the spontaneous comment that previous hypothermia has been simultaneously improved.

Conclusion

Excessive daytime sleepiness is a frequent and significant symptom of patients with Prader–Willi

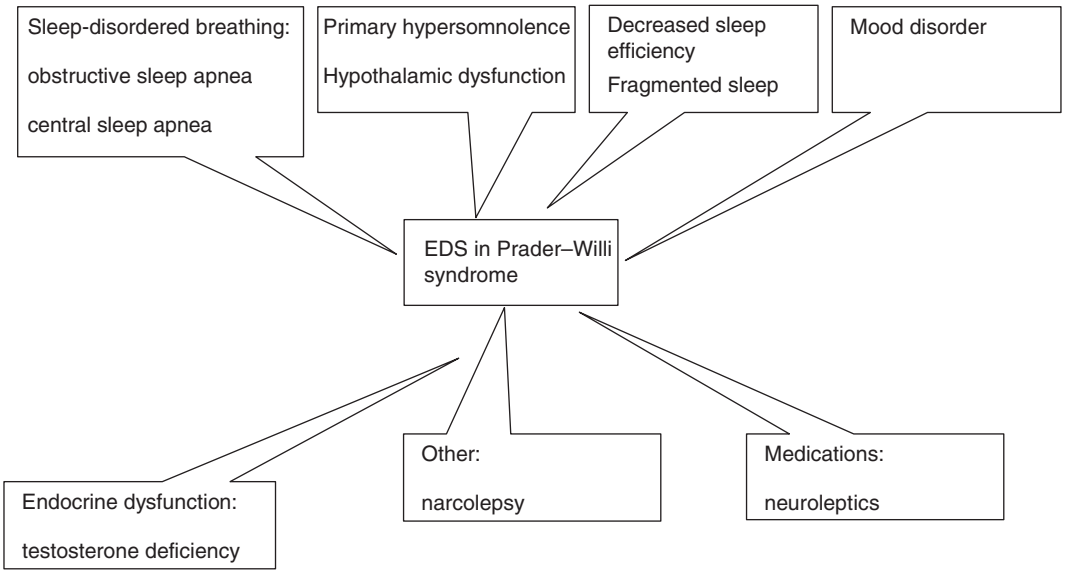

Figure 36.1 Causes of excessive daytime sleepiness in Prader–Willi syndrome.

syndrome. Patients with PWS possess a number of risk factors that predispose them to sleep-disordered breathing, but sleep-disordered breathing in itself, in many cases, cannot account for all of the daytime sleepiness experienced by such patients. A number of studies have suggested the presence of a primary hypersomnolence in PWS as evidenced by significant REM sleep dysregulation and more recently studies involving CSF hypocretin-1. Hypothalamic dysfunction is implicated in a number of symptoms characteristic of PWS, and such dysfunction likely underscores the primary hypersomnolence observed in these patients.

It is important for both the treating physician and those designing further studies to keep in mind that a number of factors have been implicated beyond those already identified (summarized in Figure 36.1). Patients with PWS, for example, are frequently put on sedating psychotropic agents for a variety of psychiatric or behavioral disturbances [23]. Prader–Willi syndrome patients may have disruptions in sleep architecture in the form of decreased sleep efficiency [19] or fragmented sleep in the form of multiple arousals or the cyclic alternating pattern (CAP). Prader–Willi syndrome is characterized by a number of endocrine abnormalities, and one author (JB) has seen at least one case where a substantial improvement in daytime sleepiness occurred in a patient with PWS following testosterone supplementation. No studies have systematically examined the effect of growth hormone deficiency itself as a cause of sleepiness.

The excessive daytime sleepiness associated with PWS is likely to be multifactorial in origin with a number of factors contributing to its expression. The complexity of hypersomnolence in PWS provides a challenge to both the treating physician and researchers, but also provides a unique insight into basic sleep–wake mechanisms.

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