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Original Article

Obstructive events in children with Prader–Willi syndrome occur predominantly during rapid eye movement sleep

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ABSTRACT

Objective: Children with Prader–Willi syndrome (PWS) have a high prevalence of obstructive sleep apnea syndrome (OSAS). In most typically developing children with OSAS, more obstructive apneas and hypopneas occur during rapid eye movement (REM) than during non-REM (NREM) sleep. It was hypothesized that patients with PWS are even more prone to obstructive events in REM sleep than otherwise healthy subjects with OSAS.

Methods: Polysomnographic data of patients with PWS and of typically developing children (controls) with OSAS (apnea–hypopnea index [AHI] > 1 episode/h) were analyzed. The two groups were compared regarding obstructive AHI (OAHI), OAHI during NREM sleep (OAHInrem), OAHI during REM sleep (OAHIrem), and the OAHIrem/OAHI ratio (outcome measures). The association between PWS diagnosis and OAHIrem/OAHI was adjusted for confounders using a general linear model.

Results: Twelve children with PWS (median age 7.1 years [interquartile range 3.5, 12.4 years]) and 53 controls (6.5 years [3.9, 8.7 years]) were studied. Children with PWS and controls were similar regarding OAHI ($p = 0.21$) and OAHInrem ($p = 0.76$). However, subjects with PWS had higher OAHIrem (17.6 episodes/h [5.8, 25.8 episodes/h]) and OAHIrem/OAHI (2.3 [1.5, 3.2]) than controls (5 episodes/h [1.5, 8.1 episodes/h]; $p = 0.002$ and 1 [0.5, 2]; $p = 0.003$, respectively). The association between PWS diagnosis and higher OAHIrem/OAHI persisted after adjustment for age, gender, and obesity ($p = 0.009$).

Conclusion: In children with PWS, OAHI calculated for total sleep time does not reflect OSAS severity during REM sleep, which on average can be twice as high. Mild OSAS in patients with PWS demonstrated by polygraphy without sleep staging may correspond to a moderately-to-severely increased OAHIrem.

1. Introduction

The majority of children with Prader–Willi syndrome (PWS) have obstructive sleep apnea syndrome (OSAS), which is of mild severity in approximately 50% of cases [1,2]. Central sleep apnea syndrome is also prevalent during the first two years of life [3–5]. Obesity, adenotonsillar hypertrophy, midface hypoplasia, micrognathia, and hypotonia, in combination with abnormal ventilatory response to hypercapnia and hypoxia, contribute to the pathogenesis of OSAS, central sleep apnea syndrome, and sleep-related hypoventilation [6–8]. Increasing OSAS severity in children with PWS is accompanied by disproportionately longer periods of hypoventilation when compared with those in typically developing children who have OSAS of similar severity [9].

Treatment with growth hormone early in life is an intervention that improves linear growth and prevents development of obesity in patients with PWS [10]. Nevertheless, severe OSAS may occur in some children while on treatment, and occurrence of sudden death has been reported [11–13]. In a retrospective study, the frequency of obstructive events increased mostly during REM sleep in a

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subgroup of patients during the first six weeks of treatment with growth hormone [14]. Consequently, polysomnography or polygraphy is recommended before and after initiation of growth hormone in order to diagnose existing or new-onset OSAS [15].

In most typically developing children, OSAS is a REM-related breathing disorder [16–18]. Hence, adequate sleep duration during polysomnography is necessary to avoid underestimation of OSAS severity, as it can occur with daytime nap studies, which may not include REM sleep periods [19]. We have hypothesized that children with PWS are more prone to obstructive events during REM sleep even before treatment with growth hormone than typically developing children with OSAS caused by adenotonsillar hypertrophy and/or obesity. As a result, the calculated frequency of obstructive events per hour of total sleep time (TST) or total obstructive apnea–hypopnea index (OAHI) in children with PWS may remarkably underestimate OSAS severity during REM sleep, and, as a result, growth hormone treatment could be commenced without prior implementation of interventions for the underlying sleep-disordered breathing.

2. Patients and methods

2.1. Inclusion and exclusion criteria for PWS patients and control subjects

Data of patients with PWS 2–18 years of age who underwent polysomnography over a three-year period and had OSAS defined as apnea–hypopnea index (AHI) $\geq$ 1 episode/h were analyzed retrospectively [20]. For comparison purposes, polysomnographic data of otherwise healthy children (controls) were also analyzed if they underwent polysomnography during the same study period due to snoring associated with adenotonsillar hypertrophy and/or obesity, and if they had OSAS.

Exclusion criteria were as follows: treatment with growth hormone; sleep in the supine position for less than 60% of TST [21–23]; any previous treatment intervention for OSAS (ie, adenoidectomy and/or tonsillectomy, continuous positive airway pressure, noninvasive positive pressure ventilation); chronic lung disease; and neuromuscular disorders or genetic diseases [18,21,24]. If a child had undergone polysomnography more than once during the study period, only the first recording was analyzed. The current retrospective study was approved by the Aghia Sophia Children's Hospital Scientific Council (no. 9539/29-04-15; approved on 13-05-15). Informed consent for use of patient data for research purposes was obtained from parents during the visit for polysomnography.

2.2. Polysomnography

The EMBLA S4500 System (Natus Medical Inc., San Carlos, CA) with REMLogic software was used. A four-channel electroencephalogram (F4/M1, C3/M2, O2/M1, O1/M2), two-channel electrooculogram, submental and tibial electromyogram, electrocardiogram, and video were recorded. Airflow was detected by thermocouples at the nose and mouth and by nasal pressure transducer, and respiratory movements were recorded using inductive plethysmography thoracic and abdominal belts. A position sensor was included. Oxygen saturation of hemoglobin (SpO2) was measured by pulse oximetry (Nonin Medical BV, Amsterdam, Netherlands). Sleep stages, arousals, and respiratory events were scored in accordance with the American Academy of Sleep Medicine recommendations by a single scorer (A.K.) [25].

AHI was calculated as the number of all apneas and hypopneas per hour of TST. For calculation of the total OAHI, central respiratory events were subtracted from the AHI. Obstructive AHI for NREM and REM sleep (OAHInrem and OAHIrem) were also calculated. A cut-off value of 5 episodes/h was used to define moderate-to-severe OSAS [20].

2.3. Outcome measures and data analysis

Outcome measures were OAHI, OAHInrem, OAHIrem, and the OAHIrem/OAHI ratio. The two study groups (PWS patients and control subjects) were compared regarding outcome measures using the Mann–Whitney *U* test for non-normally distributed continuous variables. To adjust the association between PWS diagnosis and the OAHIrem/OAHI for the effect of potential confounders, a general linear model was applied including OAHIrem/OAHI as dependent variable and PWS diagnosis, age, gender, and obesity status as explanatory variables. The square root of OAHIrem/OAHI was calculated to achieve normal distribution of values of the specific variable.

3. Results

3.1. Participants

Over the three-year study period, data of 12 subjects with PWS (median age 7.1 years; range 3–14.8 years) and 67 controls (median age 6.7 years; range 2–16.4 years) without neuromuscular or genetic disorders or chronic lung disease were studied. All 12 children with PWS and 53 of 67 controls had OSAS and slept for more than 60% of TST in the supine position. None of the 12 patients with PWS were receiving growth hormone. The two study groups were balanced in terms of AHI, % TST in REM and NREM sleep, and % REM sleep time in the supine position (Table 1).

3.2. Outcome measures

Children with PWS and controls were similar regarding OAHI and OAHInrem ($p > 0.05$) (Table 2 and Fig. 1). However, subjects with PWS had higher OAHIrem and OAHIrem/OAHI than controls ($p = 0.002$ and $p = 0.003$, respectively) (Table 2 and Fig. 1). The association between PWS diagnosis and higher OAHIrem/OAHI persisted after adjustment for obesity, age, and gender ($p = 0.009$) (Table 3). Severity of upper airway obstruction ($\leq$5 episodes/h vs >5 episodes/h) did not change in controls when the total OAHI or the OAHIrem was used (Table 1). Nevertheless, 25% of children with PWS moved from the mild to the moderate-to-severe upper airway obstruction category when the OAHIrem was used instead of the total OAHI (Table 1).

4. Discussion

In this study, we demonstrated that children with PWS have significantly higher OAHIrem, as compared to typically developing children with similar numbers of obstructive events per hour of TST. In patients with PWS, total OAHI does not reflect OSAS severity in REM sleep, and thus the OAHIrem should also be taken into consideration before initiation of treatment with growth hormone. On average, OAHIrem in PWS can be twice as high as OAHI calculated for the TST. Consequently, polygraphy without EEG and EMG channels for sleep staging, which is performed in many centers outside the United States because of limited resources, may underestimate OSAS severity in children with PWS.

In complete agreement with findings of previously published studies, 50% of children with PWS in this cohort were diagnosed with OSAS of mild severity when the total OAHI was used [1]. In contrast, 75% of patients with PWS had moderate-to-severe OSAS while in REM sleep. The vulnerability of the upper airway during REM sleep has been reported previously in an uncontrolled,

Table 1
Summary statistics regarding subjects' characteristics and polysomnography results in children with PWS and control participants.

Variables	Children with PWS, $n = 12$	Control children, $n = 53$
Age, y	7.1 (3.5, 12.4)	6.5 (3.9, 8.7)
Gender, female (%)	5 (41.7)	19 (35.8)
BMI *z*-score	2.6 (1.4, 3.2)	1 (−0.4, 1.74)
Obesity[a] (%)	9 (75)	16 (30.2)
Adenoidal hypertrophy (%)	5 (41.7)	22 (41.5)
Tonsillar hypertrophy (%)	11 (91.7)	35 (66)
TST, h	339 (251, 443)	425 (361, 450)
Time in NREM, %TST	75.5 (60, 80.2)	82 (77.7, 86.7)
Time in REM, %TST	20.7 (16.9, 29.3)	18.8 (13.7, 22.3)
% REM sleep time in supine position	64 (61, 70)	63 (61, 67)
AHI, episodes/h	5.4 (3, 14.3)	4.3 (2.3, 10.1)
Central sleep apnea index, episodes/h	0.3 (0, 1.3)	0.5 (0, 1.1)
Mean SpO_2, %	96 (93.3, 96)	97 (96, 97)
SpO_2 nadir, %	82 (72.5, 86.5)	89 (84.5, 92)
Oxygen desaturation (≥3%) of hemoglobin index, episodes/h	9.5 (4, 14.8)	4.1 (2.2, 9.2)
%TST with SpO_2 < 90%	0.8 (0.3, 2.8)	0.7 (0.1, 2.3)
Upper airway obstruction severity for TST (%)		
OAHI ≤ 5 episodes/h	6 (50)	31 (58.5)
OAHI > 5 episodes/h	6 (50)	22 (41.5)
Upper airway obstruction severity during REM sleep (%)		
OAHIrem ≤ 5 episodes/h	3 (25)	29 (54.7)
OAHIrem > 5 episodes/h	9 (75)	24 (45.3)

Continuous variables are expressed as mean ± standard deviation or as median (25th, 75th quartiles).
AHI, apnea–hypopnea index; BMI, body mass index; NREM, non-rapid eye movements sleep; OAHI, obstructive apnea–hypopnea index during total sleep time; OAHIrem, obstructive apnea–hypopnea index in rapid eye movement sleep; OSAS, obstructive sleep apnea syndrome; PWS, Prader–Willi syndrome; REM, rapid eye movement; SpO_2, oxygen saturation of hemoglobin; TST, total sleep time.
[a] Obesity was defined as BMI *z* score ≥ 1.645.

Table 2
Summary statistics and comparisons regarding outcome measures in children with PWS and control participants.

Variables	Children with PWS, $n = 12$	Control children, $n = 53$	*p*
OAHI, episodes/h	5.3 (2.1, 14)	3.3 (1.7, 9.2)	0.21[a]
OAHInrem, episodes/h	2.7 (0.7, 9.1)	3.1 (1.4, 9.1)	0.76[a]
OAHIrem, episodes/h	17.6 (5.8, 25.8)	5 (1.5, 8.1)	<0.01[a]
OAHIrem/OAHI	2.3 (1.5, 3.2)	1 (0.5, 2)	<0.01[a]

Continuous variables are expressed as median (25th, 75th quartiles).
OAHI, obstructive apnea–hypopnea index; OAHInrem, obstructive apnea–hypopnea index in non-rapid eye movement (NREM) sleep; OAHIrem, obstructive apnea–hypopnea index in rapid eye movement (REM) sleep.
[a] Mann–Whitney *U* test.

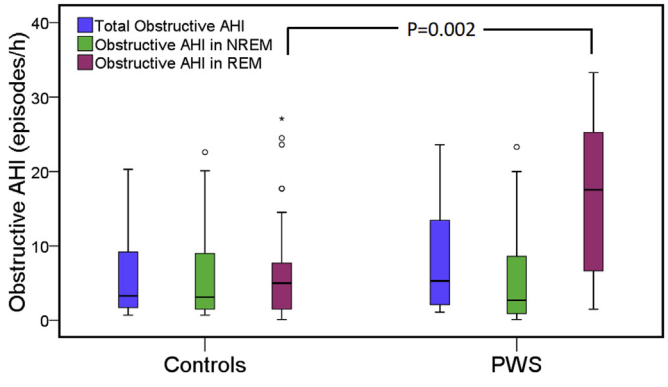

Fig. 1. Patients with Prader–Willi-syndrome have similar total obstructive apnea–hypopnea index (AHI) and obstructive AHI in non-rapid eye movement (NREM) sleep, but significantly higher obstructive AHI in REM sleep when compared to controls with obstructive sleep apnea syndrome. The upper and lower boundary of each boxplot indicate the 25th and 75th percentile values, respectively, and the heavy black line within each boxplot corresponds to the median value; the upper and lower whiskers are the largest and smallest observed values that are not outliers, whereas the round open symbols show outliers.

retrospective cohort study of 20 children with diagnosis of PWS, aged 2–21 months, who underwent polysomnography before and six weeks after the initiation of therapy with growth hormone [26].

Table 3
Estimates of the general linear model describing the association between the ratio OAHIrem/OAHI (square root of the dependent variable) and diagnosis of Prader–Willi syndrome, adjusted for the presence of obesity and other confounders.

Variables	Estimate	95% CI	*p*
Intercept	1.65	1.19–2.11	<0.01
Diagnosis			
Control	−0.44	−0.76 to −0.11	<0.01
PWS	0		
Obesity			
No	−0.15	−0.43 to 0.14	0.31
Yes	0		
Age	−0.01	−0.04 to 0.04	0.89
Gender (female = 1; male = 0)	0.13	−0.12 to 0.38	0.30

CI, confidence interval; OAHI, obstructive apnea–hypopnea index; OAHIrem, OAHI in rapid eye movement (REM) sleep; PWS, Prader–Willi syndrome.

OAHIrem was much higher than OAHInrem at baseline, while an increased number of obstructive events after initiation of growth hormone was recorded in a subgroup of participants mostly during REM sleep. Thus, focusing only on the total OAHI without simultaneously considering the OAHIrem will not allow aggressive management of OSAS in the context of treatment with growth hormone.

The main pathogenetic abnormality of PWS is the loss of paternal expression of several imprinted genes located on the

15q11–q13 chromosome region, including the gene for NECDIN protein [27]. Respiratory abnormalities in the NECDIN-deficient mice (frequent central apneas, respiratory rhythm irregularity, and blunted respiratory responses to hypoxia and hypercapnia) resemble the clinical features of PWS in humans [28,29]. Abnormal control of breathing is not the sole factor contributing to OSAS pathogenesis and to the high risk of ventilatory failure in PWS [30]. The unremitting hunger related to the syndrome leads to severe or morbid obesity, which increases upper airway collapsibility and the frequency of obstructive sleep apneas and hypopneas [1,31].

Growth hormone treatment has been offered to patients with PWS in an effort to improve linear growth and to delay or inhibit the development of obesity [10]. Nevertheless, severe OSAS may occur in some patients while on treatment and especially during episodes of respiratory infections, and cases of sudden death have been reported [11–13]. Growth hormone does not improve the ventilatory response to hypercapnia during sleep, and there are also concerns that it may actually promote growth of adenotonsillar tissue and upper airway obstruction [32].

In an Italian cohort study, children with PWS younger than eight years who did not have OSAS or severe obesity were started on treatment with growth hormone and were subsequently monitored for 48 months [11]. Progressive enlargement of adenotonsillar tissue and a rise in OAHI resulted in some patients requiring adenotonsillectomy and temporary or permanent discontinuation of growth hormone therapy. Therefore, exclusion of existing or new-onset OSAS by polysomnography before and after commencement of growth hormone therapy is of paramount importance because nocturnal upper airway obstruction would increase the mechanical respiratory load and possibly the risk of sleep-related hypoventilation [9,15]. We speculate that at least some of the patients who develop OSAS while receiving growth hormone already have undiagnosed OSAS in REM sleep at baseline [11,12,14,26].

Currently, there are no recommendations on how to manage patients with PWS who have an OAHI < 1 episode/h but an elevated OAHIrem. In our cohort of children with PWS, all subjects had at least mildly elevated OAHI, and thus they received appropriate treatment regardless of the OAHIrem. In future studies, the potential importance of an abnormal OAHIrem as risk factor for OSAS development after treatment with growth hormone needs to be explored.

In this study, a control group of otherwise healthy children with OSAS was used for comparison purposes. Since the results of studies on the effect of body position on frequency of obstructive events during sleep in children are conflicting, we have analyzed data of subjects who slept in the supine position for the majority of TST to minimize this effect [17,18,21–23]. We recognize that the number of patients with PWS was relatively small. Only half of the children in the control group had higher OAHIrem than the OAHI. Obstructive events occur more predominantly in REM than in NREM sleep in approximately 70% of children, and this proportion is affected by sleep position [17,18]. However, the control subjects in this study slept mostly in the supine position, which is characterized by predominance of REM obstructive events over NREM events in approximately 50% of cases [18].

5. Conclusion

In conclusion, in children with PWS, OAHI calculated for TST underestimates OSAS severity during REM sleep appreciably, which on average can be twice as high. Calculation of OAHIrem in addition to total OAHI is necessary in sleep studies that are performed before and after initiation of growth hormone in PWS patients, so that OSAS is recognized in a timely manner and treated. Mild OSAS evaluated by polygraphy may correspond to a moderately-to-severely increased OAHIrem when calculated by polysomnography, and thus appropriate treatment interventions should be considered.

Conflicts of interest

The ICMJE uniform disclosure form for potential conflicts of interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.026.

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