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Obstructive sleep apnea and otolaryngologic manifestations in children with pseudohypoparathyroidism

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Abstract

Background/Aims: Pseudohypoparathyroidism type (PHP) is a rare, genetic disorder. Patients with PHP may have increased prevalence of obstructive sleep apnea (OSA) but this has not been prospectively studied.

Methods: We enrolled children 6–18 years old with PHP and matched controls. Evaluation included physical exam, medical history and polysomnography.

Results: Fifteen PHP type 1A (PHP1A) and 15 controls completed the study. Both groups were obese (BMI 32.2±8.7kg/m^2 vs. 31.7± 6.5kg/m^2). The majority of PHP1A patients required tympanostomy tubes (86.7%) and adenotonsillectomy (73.3%). The primary outcome, obstructive disturbance index, was significantly higher in PHP1A vs. controls (1.8±2.3 vs. 0.6±0.5, p = 0.045). Children with PHP1A were more likely to have OSA compared with controls (60.0% vs.13.3%, p=0.008). Three siblings with PHP type 1B (PHP1B) were also studied (BMI 25.9 ± 9.0kg/m^2). None had a history of adenotonsillectomy, one had tympanostomy tubes. The obstructive disturbance index (2.0±2.3) was similar to PHP1A. Two (66.7%) PHP1B participants had OSA.

Conclusion: Children with PHP1A are at an increased risk for OSA compared with similarly obese peers. They also have higher rates of otitis media and adenotonsillar hypertrophy. Screening for OSA should be considered in all patients with PHP1A and possibly PHP1B though more research is needed.

Keywords

pseudohypoparathyroidism; sleep apnea

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Introduction

Pseudohypoparathyroidism (PHP) is an uncommon disorder resulting from decreased activity of the alpha subunit of the stimulatory G-protein ($G_s\alpha$). PHP type 1a (PHP1A) results from maternal inheritance of inactivating mutations in *GNAS* or de novo mutations on the maternal allele. In most tissues, these mutations result in a 50% reduction of normal $G_s\alpha$ activity, consistent with biallelic expression of *GNAS*. [1] In other tissues, notably the pituitary and the thyroid, the maternal *GNAS* allele is dominantly expressed. Thus, maternal inheritance of a mutant allele leads to a dramatic decrease in the amount of functional $G_s\alpha$ present in these tissues. Individuals with PHP1A exhibit multi-hormone resistance and Albright's Hereditary Osteodystrophy, a recognizable phenotype characterized by short stature, obesity, brachydactyly, and subcutaneous ossifications. [2] PHP type 1b (PHP1B) most often results from methylation defects at the maternal *GNAS* locus and is characterized by resistance to PTH. [3] Though it was initially thought that individuals with PHP1B did not display the physical abnormalities seen in PHP1A, there is recent evidence of overlapping phenotype between the two disorders. [4]

Individuals with PHP1A commonly experience early-onset obesity and are at risk for obesity-related conditions, including insulin resistance and diabetes. [5, 6] Our previous work has shown that children with PHP1A may be at an even greater risk for obstructive sleep apnea (OSA) than similarly obese children but this study was limited to a retrospective review of medical records. [7] Despite the recent evidence of clinical overlap between PHP1A and PHP1B, it is not known if individuals with PHP1B have an increased risk of OSA.

Sleep apnea has been associated with cognitive dysfunction, cardiovascular disease, and altered glucose metabolism.[8, 9] These complications may be particularly harmful to individuals with PHP1A, who are predisposed to cognitive impairment, early-onset obesity, and diabetes. [5, 6, 10, 11] It is important to accurately determine the risk of OSA in individuals with PHP1A and PHP1B in order to guide screening decisions and encourage appropriate intervention. This study aimed to prospectively investigate the relationship between PHP1A/PHP1B and sleep apnea in children using polysomnography, a gold standard for evaluating sleep disordered breathing.

Methods

Participants:

Participants with PHP1A were recruited from Vanderbilt Pediatric Endocrinology Clinics and from across the United States and Canada using online advertisements. Inclusion criteria were: age between 6 and 18 years old and a clinical diagnosis of PHP1A with multi-hormone resistance. Exclusion criteria included: diagnosis of diabetes mellitus, current treatment with an appetite-altering drug, or recent initiation of a new weight loss program.

Controls were recruited from the Vanderbilt Childhood Obesity Registry and Vanderbilt Pediatric Clinics. Controls were recruited to match PHP1A participants for gender, race, age (± 2 years), and BMI (± 2 kg/m^2). Exclusion criteria were: obesity due to an underlying

genetic syndrome or hormonal imbalance, current treatment with an appetite-altering drug, recent initiation of a new weight loss program, >10% weight loss over the past 6 months, diagnosis of diabetes mellitus, or another significant medical condition.

Informed consent or parental consent and child assent were obtained prior to enrollment. The study was approved by the Institutional Review Board of Vanderbilt University Medical Center.

Experimental Procedure:

Subjects were asked to maintain a normal diet and abstain from strenuous exercise and caffeine in the 3 days prior to testing. Weight was determined using a digital scale and height was measured using a wall-mounted stadiometer (measured in light clothing without shoes). A physician performed a physical exam for each participant and elicited a medical history and family medical history. Participants were given a standardized buffet-style meal between 5pm and 6pm and were allowed a small, standard snack between 8pm and 10pm if desired. All participants were asked to be in bed by 10pm. Polysomnography was performed overnight to evaluate for obstructive and central sleep apnea. Participants were allowed to use their home CPAP or BiPAP if applicable. Participants were awakened between 6am and 7am.

Polysomnography:

Overnight polysomnography (PSG) with video was performed at the Vanderbilt Clinical Research Center. Digital PSG diagnostic systems (Neurofax EEG-1100, Polysmith 6.0, Nihon-Kohden, Irvine, CA) and Sandman Digital 32+ Amplifier (Sandman, Elite Sleep Diagnostic Software, Natus Medical Embla, San Carlos, CA) were used to analyze sleep.

The American Academy of Sleep Medicine (AASM) guidelines were followed for the collection of PSG data. [12] Neurophysiological channels included two frontal (F3 and F4), two central (C3 and C4), and two occipital (O1 and O2) EEGs referenced to common electrodes (M2 and M1, respectively), chin electromyography (EMG), and electrooculography (EOG) E1 and E2. Limb movements were monitored using EMG placement on the anterior tibialis of each leg. Cardiorespiratory data were collected using inductive plethysmography with non-calibrated sum signal to monitor respiratory effort of both the chest and abdomen. Airflow was measured by both nasal pressure cannula and by oral/nasal thermocouple. Pulse oximetry signal (SpO_2) was recorded to monitor oxygen saturations. A lead II electrocardiogram (ECG) was used to monitor heart rhythm.

PSG data were classified for stages wake (W), non-rapid eye movement sleep N1, N2, N3, and rapid eye movement sleep (REM) following standard AASM guidelines. [13] Sleep Efficiency (SE) was defined as the percentage of total sleep time to total time in bed. A single registered polysomnography technologist performed the staging to avoid inter-rater reliability concerns. A board-certified sleep specialist reviewed each study to ensure accuracy. Both reviewers were blinded to patient group.

Data Collection:

Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies[13].

Statistics:

The primary outcome of interest was the obstructive disturbance index (ODI), the number of apnea/hypopnea episodes per hour excluding central apneas. Results are presented as mean ± standard deviation. Continuous variables were compared using Student's t test. Categorical variables were compared using Chi-square test. Statistics were performed using the SPSS version 24.

Results

Enrollment

Nineteen patients with PHP1A/1B and fifteen controls were enrolled in the study. Patients were divided into PHP1A (n=16) and PHP1B with multi-hormone resistance (n=3) groups based on genotype. A detailed description of the genotype and phenotype of the PHP1A group has been previously published [11]. The three PHP1B patients were siblings with a 3kb STX16 deletion, a previously described mutation. [14] All PHP1B patients had PTH and TSH resistance, two were obese and one was normal weight. None of the PHP1B patients had subcutaneous ossifications, brachydactyly or short stature. The polysomnography equipment malfunctioned for one participant with PHP1A and he was excluded from the study (final PHP1A group, n=15). Two PHP1A participants had clinical OSA requiring BiPAP. One was diagnosed 3 years prior after demonstrating an apnea hypopnea index of 5.2. The second patient was diagnosed 2 years prior after demonstrating an apnea hypopnea index of 20.2 and an ODI of 10.0. As we did not conduct polysomnography without their home BiPAP, these participants are included only in the dichotomous analyses.

PHP1A

Table 1 summarizes the baseline demographic characteristics. All participants were white. The PHP1A group and control group were well matched on age, gender and BMI. The PHP1A and control groups were obese, with BMIs of 32.2 ± 8.7 and 31.7 ± 6.5 respectively. The PHP1A group was significantly more likely to have a history of asthma, frequent otitis media, hearing problems and hypotonia (Table 2). The majority of PHP1A patients required tympanostomy tube placement (86.7%) and adenotonsillectomy (73.3%) during childhood (Table 2).

Polysomnography results are detailed in Table 3. The primary outcome, obstructive disturbance index (ODI), was significantly different between participants with PHP1A (n = 13) and controls (1.8 ± 2.3 vs. 0.6 ± 0.5, p = 0.045). We used an ODI ≥1 as the a priori cutoff for OSA. Children with PHP1A were more likely to have OSA than controls (60.0% vs.13.3%, n=15, p=0.008). Participants with PHP1A (n = 13) spent a significantly less time in REM sleep compared with controls (11.1 ± 5.3% vs. 16.5 ± 4.2%, p= 0.006). Eight

(88.9%) of the PHP1A participants with OSA diagnosed by polysomnography had already undergone adenotonsillectomy and 7 (77.8%) had a previous asthma diagnosis.

PHP1B

As our PHP1B cohort was limited to a single family, they are presented separately and without a control group. The PHP1B group had an average BMI of 25.9 ± 9.0. None of the patients had a history of asthma or adenotonsillectomy. One of the three siblings had a history of tympanostomy tubes. No patients reported a history of hypotonia. The polysomnography results were similar between the PHP1B and PHP1A groups with an average ODI of 1.8 ± 2.3 and 2.0 ± 2.3 respectively. Two (66.7%) PHP1B participants had OSA. PHP1B participants spent an average of 13.5 ± 5.3% of the sleep period in REM sleep.

Discussion

This is the first prospective study utilizing overnight polysomnography to investigate the presence of sleep apnea in children with PHP1A compared with controls. Our study adds to the evidence indicating that children with PHP1A are at an increased risk for OSA compared with healthy children and similarly obese peers. While an estimated 1–5% of children and 8% of obese children have sleep apnea , we found clinically significant OSA demonstrated by polysomnography in 60% of children with PHP1A. [15, 16] We also found sleep apnea in 2 of 3 children with PHP1B, though a larger sample of children with PHP1B is required before conclusions can be drawn for this population.

Obesity is an independent risk factor for OSA, increasing the risk nearly 3-fold in obese children compared with non-obese children. [17] Though PHP1A participants in this study were obese, by design there were no differences in the rate or severity of obesity between PHP1A participants and control participants. Despite this, participants with PHP1A had a 4-fold increased relative risk of OSA. Thus, the high prevalence of obesity in children with PHP1A cannot fully explain the increased risk of sleep apnea in this population. Furthermore, the PHP1B group was not obese and still showed increased rates of OSA compared with the general population, though further research is needed before generalizing our results to all patients with PHP1B.

Children with PHP1A seem to have increased rates of asthma compared to the general population. [7, 18, 19] In adults, asthma has been associated with the development of OSA. [20] In this study, asthma was more prevalent in the PHP1A group than in the control group and may account for the increased risk of OSA in this population.

OSA results from sleep-induced airway collapse and subsequent hypoventilation. In this study, a history of hypotonia was observed only in the PHP1A group. It is conceivable that the hypotonia observed in children with PHP1A may be related to the increased risk of sleep apnea seen in this population, similar to what is seen in patients with Down syndrome. [21] In fact, some clinical features of Down syndrome and PHP1A overlap. With both disorders, there is a high prevalence of recurrent otitis media requiring typanostomy tubes, an increased rate of hearing loss, and a high risk of sleep apnea. [7, 19, 21] These clinical features were evident in our PHP1A sample and may indicate craniofacial abnormalities in

children with PHP1A similar to those documented in Down syndrome. [21] These possible anatomical abnormalities, combined with generalized hypotonia, may lead to the increased rates of sleep apnea seen in individuals with PHP1A, though further research regarding the hypotonic and craniofacial phenotype in this population is needed.

Untreated sleep apnea can have serious consequences, including cardiovascular morbidity, glucose metabolism disturbances, executive dysfunction, and problems with attention.[8, 9] Sudden death has not been reported in PHP1A, but young children with other congenital syndromes and sleep apnea are at increased risk of sudden death from respiratory insufficiency.[22, 23] These cognitive impairments, in addition to the symptoms of sleep apnea such as daytime somnolence, may lead to poor academic performance. In fact, treatment of childhood sleep apnea has been shown to improve behavior, school performance, and quality of life. [24, 25] While adenotonsillectomy is the first-line treatment of OSA in pediatric populations, almost all of the PHP1A participants demonstrating clinically significant apnea in this study had already undergone adenotonsillectomy. Therefore, treatment with CPAP or BiPAP should be considered in this population.

It is worth noting that disordered sleep may be part of the PHP1A phenotype. PHP1A results from decreased $G_s\alpha$ activity, usually due to mutations involving the encoding gene *GNAS.* [3] Murine models have shown the importance of *Gnas* in regulating sleep architecture, particularly with regards to REM sleep. Increased *Gnas* mRNA expression was shown to inhibit REM sleep in mice. [26] In our study, participants with PHP1A spent a significantly smaller proportion of time in REM sleep than controls. It is plausible that abnormal sleep patterns observed in children with PHP could be related to decreased *GNAS* expression and decreased $G_s\alpha$ activity.

In summary, this report adds to the evidence that there is an increased prevalence of sleep apnea in children with PHP1A compared with similarly obese peers. Appropriate screening and prompt intervention may improve health outcomes and academic performance in children with PHP1A. We recommend considering polysomnography in patients with PHP1A, particular young children and those with a history of asthma or snoring. Though it appears there may be an increased risk of OSA in children with PHP1B compared with the general population, our results are limited to 3 patients from one family and further research is needed before we recommend evaluation of OSA in children with PHP1B.

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Table 1:

Baseline patient characteristics of PHP1A, PHP1B and control groups. P value compares PHP1A and control groups by Chi-square test (dichotomous values) or Student's t-test (continuous values)

	PHP1A (n=15)	PHP1B (n=3)	Controls (n=15)	p-value
n (%)				
Sex				
Female	10 (66.7)	1 (33.3)	11 (73.3)	0.69
Ethnicity				
Hispanic	1 (6.7)	0	2 (13.3)	0.54
Mean ± SD				
Age (years)	12.8 ± 2.5	13.0 ± 3.0	12.5 ± 2.3	0.76
BMI (kg/m^2)	32.2 ± 8.7	25.9 ± 9.0	31.7 ± 6.5	0.87
Body Fat* (%)	44.9 ± 6.1	41.9 ± 9.5	46.6 ± 4.5	0.40

* n=14 PHP1A

Table 2:

Relevant medical history. P value compares PHP1A and control groups by Chi-square test.

	PHP1A (n=15)	PHP1B (n=3)	Controls (n=15)	p-value
n (%)				
Asthma	10 (66.7)	0	1 (6.7)	**0.001**
Snoring	12 (80.0)	1 (33.3)	4 (26.7)	**0.003**
Adenotonsillectomy	11 (73.3)	0	6 (40.0)	0.07
Ear infections	13 (86.7)	1 (33.3)	4 (26.7)	**0.001**
Hearing problems	7 (46.7)	1 (33.3)	0	**0.003**
Typanostomy tubes	13 (86.7)	1 (33.3)	2 (13.3)	**<0.001**
Hypotonia	10 (66.7)	0	0	**<0.001**

Table 3:

Overnight polysomnography data from PHP1A, PHP1B and control groups. P value compares PHP1A and matched control groups by Chi-square test (dichotomous values) or Student's t-test (continuous values)

Mean ± SD	**PHP1A (n=13)**	**PHP1B (n=3)**	**Controls (n=15)**	**p-value**
ODI	1.8 ± 2.3	2.0 ± 2.4	0.6 ± 0.5	**0.045**
Minimum SaO2 during REM sleep, %	90.1 ± 5.2	92.0 ± 1.7	89.8 ± 2.8	0.86
WASO, %	6.1 ± 3.7	16.9 ± 6.8	8.1 ± 6.6	0.35
N1 sleep, %	2.0 ± 1.4	15.6 ± 7.6	3.2 ± 2.2	0.12
N2 sleep, %	57.4 ± 7.8	45.7 ± 7.1	55.0 ± 8.3	0.44
N3 sleep, %	29.5 ± 8.1	25.2 ± 2.0	25.4 ± 9.2	0.22
REM sleep, %	11.1 ± 5.3	13.5 ± 5.3	16.5 ± 4.2	**0.006**
n (%)	PHP1A (n=15)	PHP1B (n=3)	Controls (n=15)	
OSA	9 (60.0)	2 (66.7)	2 (13.3)	**0.008**

ODI, obstructive disturbance index; SaO2, percent oxygen saturation; REM, rapid eye movement; WASO, wake after sleep onset