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Increased Prevalence of Sleep Apnea in Children with Pseudohypoparathyroidism Type 1a

Hannah Landreth[1], **Beth A. Malow, MD**[2], and **Ashley H. Shoemaker, MD, MSCI**[3]

[1]University of Oklahoma School of Medicine

[2]Vanderbilt University, Department of Neurology

[3]Vanderbilt University, Department of Pediatrics, Division of Endocrinology

Abstract

Background/Aims—Pseudohypoparathyroidism type 1a (PHP1a) is a rare genetic disorder. This study aimed to determine the prevalence of sleep apnea in children with PHP1a.

Methods—Nineteen patients with PHP1a between 2 and 21 years old were enrolled prospectively using online advertisements. Parents completed a medical history and surveys to assess sleep behavior. Polysomnography records were obtained when available. In addition, 18 subjects were identified in a retrospective chart review of de-identified medical record with 2.3 million patient charts.

Results—Parents reported sleep disturbance (94%) and daytime somnolence (81%) in their child with PHP1a. In the retrospective chart review, 39% had a history of sleep apnea versus 8.8% of a similarly obese control group. In the combined analysis (n= 31), 52% had a history of snoring and 45% had a diagnosis of sleep apnea. Patients were obese with a mean BMI z-score of 2.20 ± 0.59. Patients with sleep apnea were significantly younger than those without a diagnosis (8.1 ± 5.4 vs. 12.8 ± 5.0 years, p= 0.02).

Conclusions—Children with PHP1a have a 4.4 fold greater relative risk of sleep apnea than similarly obese children. Screening for sleep apnea in this population may be warranted to prevent adverse health outcomes.

Keywords

Rare genetic syndromes related to endocrinology; pediatric endocrinology; obesity; sleep apnea; sleep and endocrinology; Albright Hereditary Osteodystrophy; pseudohypoparathyroidism type 1a

Address: Ashley H. Shoemaker, MD, MSCI, 2200 Children's Way, DOT 11133, Nashville, TN 37232-9170, Ph: 615-343-8116, Fax: 615-875-7633, Ashley.H.Shoemaker@vanderbilt.edu.

Introduction

Pseudohypoparathyroidism is a rare genetic disorder caused by mutations in the gene *GNAS* which encodes the alpha subunit of the stimulatory G-protein. In some tissues, such as the pituitary, hypothalamus and thyroid, *GNAS* is imprinted and the maternal allele is preferentially expressed. Maternally inherited mutations therefore lead to the most severe phenotype, known as pseudohypoparathyroidism type 1a (PHP1a). PHP1a is characterized by multi-hormone resistance, obesity, cognitive impairment and the Albright Hereditary Osteodystrophy (AHO) phenotype. The AHO phenotype is readily identifiable and includes short stature, brachydactyly, round facies and subcutaneous ossifications.

Patients with PHP1a are cared for by pediatric endocrinologists. In order to provide optimal care for these patients, it is critical that we understand the phenotype of PHP1a and appropriately manage all comorbidities. Children with PHP1a typically have early-onset obesity and may be at high risk for obesity related comorbidities. Based on the clinical observation of frequent sleep apnea in this population, this study aimed to determine the prevalence of sleep apnea in children with PHP1a. In order to accomplish this aim, we conducted a prospective study of children with PHP1a using a sleep quality survey and medical record review. In addition, we conducted a retrospective chart review of all patients treated for PHP1a at a single institution.

Methods

Participants

Study participants with pseudohypoparathyroidism type 1a (PHP1a) were recruited from the Vanderbilt University adult and pediatric endocrinology clinics and online advertisements (www.facebook.com/pseudohypoparathyroidism) from April to August of 2014. Inclusion criteria were age ≥2 years old and English proficiency. Informed consent or parental consent and age appropriate assent were obtained prior to enrollment. The study was approved by the Institutional Review Board (IRB) of Vanderbilt University.

The retrospective chart review utilized the Vanderbilt University Synthetic Derivative, a de-identified electronic medical record containing approximately 2.3 million patient records updated through August 31, 2013. This was reviewed by the IRB of Vanderbilt and determined to be non-human subject research. Patients were included if they had a diagnosis of PHP1a and had at least one visit in the pediatric endocrinology clinic, as determined by manual chart review.

Experimental Procedure

Study data were collected using REDCap (Research Electronic Data Capture) [1] online surveys hosted at Vanderbilt University. All participants completed a medical history form. Participants who reported a history of polysomnography were asked to provide copies of the polysomnography reports to research personnel.

Parents of children less than 18 years old completed an abbreviated version of the Children's Sleep Habits Questionnaire (CSHQ, see supplement). The original CSHQ included 33 items.

[2] The abbreviated version used in our study included 18 items graded on a 1 to 5 scale (1 = always, 5 = never). This version was developed by the University of Wisconsin, Madison as part of the National Institute of Child Health and Human Development Study of Early Child Care and Youth Development.

The Vanderbilt University Synthetic Derivative was searched for records containing a parathyroid hormone level and the keywords “pseudohypoparathyroidism” or “Albright Hereditary Osteodystrophy” and diagnosis was confirmed by manual review of the chart. We recorded demographic information, number of clinic visits, history of growth hormone treatment, history of asthma, history of snoring, polysomnography records, diagnosis of sleep apnea and use of CPAP or BiPAP. The BMI z-score was calculated from the height and weight at the most recent endocrine clinic visit. For a comparison group, we also estimated the prevalence of obstructive sleep apnea in children 0 – 21 years old with a BMI >30 kg/m^2 based on the presence of either an ICD9 code for sleep apnea (327.2, 327.20 and 327.23) or the keywords “sleep apnea” or “OSA” in the medical record problem list.

Statistics

For the analysis of the two groups combined, we excluded the Vanderbilt University patients enrolled in the prospective study as their results were likely duplicated in the de-identified medical records of the retrospective chart review. Results are presented as mean ± standard deviation. Continuous variables were compared using Student’s t-test. Categorical variables were compared using Fisher’s Exact test. Statistics were performed using SPSS version 22.

Results

Prospective Study

Nineteen patients between 2 and 21 years old enrolled in the prospective study, including 6 males and 13 females. Baseline characteristics are detailed in table 1. The average age was 10.4 ± 5.2 years old (range 2 to 21 years). All patients were currently treated with levothyroxine, calcium and calcitriol. Two males were currently treated with growth hormone. Six patients (2 males and 4 females) had a history of asthma. The patients were obese with a mean BMI z-score of 2.24 ± 0.60 (n= 16).

Habitual snoring was reported in 10 of 19 of patients (53%). Fourteen patients had undergone polysomnography for evaluation of sleep apnea and 11 were diagnosed with sleep apnea. Five patients were currently using CPAP or BiPAP for treatment of sleep apnea. Of the 5 patients who had not been formally evaluated for sleep apnea, 2 reported habitual nighttime snoring. Fourteen children had undergone polysomnography and records were obtained from 9 children. Review of these records showed that 2 patients had no significant apnea, 1 patient had central and obstructive apnea, 3 patients had central apnea only and 3 patients had obstructive apnea only. Sleep architecture was disrupted in 5 children with increased NREM Stage 1 sleep, decreased REM sleep and prolonged REM latency. The obstructive apnea was moderate to severe (pre-treatment Apnea Hypopnea Index (AHI) >5). The patients with obstructive apnea all had adenotonsillectomy without

resolution of symptoms; 3 of 4 children continued to require CPAP or BiPAP postoperatively.

Children's Sleep Habits Questionnaire

Sixteen parents completed the CSHQ on behalf of their child. The average total score was 2.1 ± 0.4 (range 1.4 – 3.2). There was not a significant difference in total score between unaffected children (n= 6), children with sleep apnea not currently treated (n= 5) and children treated with CPAP or BiPAP (n=5) (2.0 ± 0.3 vs. 2.01 ± 0.2 vs. 2.2 ± 0.6, p= 0.74 by one-way ANOVA). Three questions had average scores >3; a score of 3 means symptoms occur 2-4 times per week and a score of 4 means symptoms occur 5-6 times per week. The highest scoring questions include "child is restless and moves a lot during sleep" (3.8 ± 1.0) "child awakens once during the night" (3.0 ± 1.4) and "child seems tired during the daytime" (3.1 ± 1.3). Fifteen of sixteen children (94%) had scores of 3 or greater in the area of sleep disturbance and 13 of 16 (81%) had scores of 3 or greater for daytime somnolence. The children slept an average of 10.3 ± 0.9 hours on weeknights and 11.4 ± 1.1 hours on weekends. Three children 2-4 years old napped 2 hours per day, a 6 year old child napped 1.5 hours per day and a 7 year old child napped 0.5 hours per day.

Retrospective Chart Review

The Synthetic Derivative search identified 145 charts (out of 2.3 million) for manual review. Eighteen patients were identified with a diagnosis of PHP1a for an overall prevalence of 1 in 125,000 patients. Patients had an average of 10.3 ± 7.1 (range 1 – 25) endocrine clinic visits available for review. There were no significant differences between the prospective and retrospective cohorts. Baseline characteristics are described in table 1. The patients were an average of 11.1 ± 5.5 years old (range 2 – 21 years) at the time of the last clinic visit. Two females had been treated with growth hormone prior to reaching their final adult height. Half of the patients had a history of asthma. Patients were obese with an average BMI of 31.8 ± 8.5 kg/m^2 (n= 17) and a BMI z-score of 2.26 ± 0.53 (n= 16). One 30 month old patient did not have a height recorded but the weight z-score was 4.11. Another patient was 17 months old at last visit with a weight z-score of 2.01 (cannot calculate BMI z-score for children <2 years old).

Half of the patients had a history of snoring noted in the medical record. Eight patients had adenoidectomy ± tonsillectomy for symptoms of sleep apnea. Nine patients had undergone polysomnography for evaluation of sleep apnea and 7 were diagnosed with clinically significant sleep apnea. Six were noted to have disrupted sleep architecture, particularly decreased REM and prolonged REM latency. Four patients had documented use of CPAP or BiPAP for treatment of sleep apnea despite previous adenotonsillectomy. In the Synthetic Derivative, 28,340 children between 2 and 21 years old have a BMI >30 kg/m^2. Of those children, 2,500 had a diagnosis of obstructive sleep apnea based on our search terms; therefore the estimated prevalence of obstructive sleep apnea in obese children was 8.8%. In the same database, the prevalence of sleep apnea in children with PHP1a was 39%. The relative risk of sleep apnea was 4.4 fold greater in children with PHP1a compared with other obese children at our institution.

Combined Analysis

Thirty one subjects were included in the combined analysis of the prospective and retrospective studies as data from Vanderbilt University patients were only included once. The baseline characteristics of the combined group are detailed in table 2. The average age was 10.7 ± 5.6 years old. Twelve patients (39%) had a diagnosis of asthma. 16 patients (52%) had a history of snoring and 14 patients (45%) had a diagnosis of sleep apnea. Children diagnosed with sleep apnea were significantly younger than those without a diagnosis (8.1 ± 5.4 vs. 12.8 ± 5.0 years, p= 0.02). There was no significant difference in gender, BMI z-score or growth hormone treatment between groups (table 3). Children with sleep apnea were more than twice as likely to have been diagnosed with asthma, but this did not reach statistical significance (57% vs. 24%, p= 0.08).

Discussion

To our knowledge, this is the first report on sleep apnea in PHP1a. We found an unusually high prevalence of patients with sleep apnea as diagnosed by polysomnography. Sleep apnea is reported in 1%-5% of otherwise healthy children versus 45% of children with PHP1a in our combined analysis [3, 4]. Habitual snoring is a sensitive, but less specific, marker of obstructive sleep apnea in children. Several patients with PHP1a who had not been formally evaluated for sleep apnea reported habitual snoring and further evaluation may reveal an even higher prevalence of apnea in this population.

Obstructive sleep apnea is much more common in obese children with a reported prevalence of 5-8% for moderate-severe apnea (AHI >5) [5, 6], however, we found a 4.4 fold increase in relative risk of sleep apnea in children with PHP1a compared with similarly obese children. The high rate of sleep apnea in children with PHP1a (45%) is only partially attributable to the concomitant obesity. All patients were obese and there was not a significant difference in the severity of obesity between those with and without a diagnosis of sleep apnea. In addition, obesity does not explain the cases of central sleep apnea found in our cohort as central sleep apnea may be less common in obese children [7]. It is not clear why the children with sleep apnea were significantly younger than those without a diagnosis of sleep apnea. One possibility is that pediatricians now have an increased awareness of sleep apnea due to the obesity epidemic and are more commonly screening for symptoms. Younger children are followed more closely by pediatricians and there may be more opportunities to elicit symptoms. Asthma is associated with the risk of developing obstructive sleep apnea in the general population [8] and the majority of patents with PHP1a and sleep apnea also carried a diagnosis of asthma.

It is possible that sleep apnea and sleep disordered breathing is another clinical manifestation of PHP1a. PHP1a occurs due to inactivating mutations in *GNAS* and the resultant abnormal Gs-protein coupled receptor signaling. In the murine model, *Gnas* overexpression inhibits REM sleep and underexpression, as seen in PHP1a, may be similarly disruptive to normal sleep architecture. Disruption of sleep architecture may contribute to the daytime somnolence and restless sleep reported by these patients [9]. The neuromuscular phenotype has not been investigated, but children with PHP1a have significant gross and

fine motor milestone delays requiring physical and occupational therapy (unpublished data). Hypotonia in this population may also contribute to development of obstructive sleep apnea.

Excessive daytime sleepiness, untreated sleep apnea and sleep disordered-breathing, as reported in our cohort, is associated with poor memory and concentration [10, 11]. Treatment of sleep disordered breathing and sleep apnea may improve attention and school performance [12–14]. Diagnosis and treatment of sleep apnea may be particularly beneficial for children with PHP1a as the majority have baseline cognitive impairment and school difficulties [15]. Obstructive sleep apnea is associated with an increased risk of heart disease and may alter glucose metabolism [16]. These associations are concerning for patients with PHP1a as the disease is known to cause early-onset obesity and insulin resistance [17, 18].

Our study was limited by the small sample size. It is possible that there was selection bias with patients more likely to participate in the prospective study if they had a diagnosis of sleep apnea. In addition, the sleep apnea prevalence of 39% in our retrospective cohort may be artificially low as five of the patients had three or fewer visits to our clinics and pediatric endocrinologist may not address sleep disorders at a routine appointment.

Children with PHP1a may require treatment with growth hormone due to resistance to growth hormone releasing hormone. In Prader-Willi syndrome, treatment with growth hormone has been associated with fatal obstructive sleep apnea, possibly due to increased adenotonsillar hypertrophy or concurrent respiratory infections [19]. While adenotonsillectomy did not resolve obstructive sleep apnea in the majority of our cohort, similarly high rates of treatment failure have been seen in children with common obesity [20]. CPAP and BiPAP, however, were effective treatments in our cohort and should be considered before initiating growth hormone therapy.

In summary, we found an increased prevalence of sleep apnea in PHP1a compared with similarly obese children. Early detection and intervention for sleep apnea could improve quality of life and prevent adverse health outcomes in this vulnerable population.

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Wisconsin Abbreviated Children's Sleep Habits Questionnaire

The following statements are about your child's sleep habits and possible difficulties with sleep. Think about the past week in your life when you answer the questions. If last week was unusual for a specific reason, choose the most recent typical week. Unless noted, check Always if something occurs every night, Usually if it occurs 5 or 6 times a week, Sometimes if it occurs 2 to 4 times a week, Rarely if it occurs once a week, and Never if it occurs less than once a week.

1. Child goes to bed at the same time at night*
2. Child falls asleep within 20 minutes after going to bed*
3. Child falls asleep alone in own bed*
4. Child falls asleep in parent's or sibling's bed
5. Child falls asleep with rocking or rhythmic movements
6. Child needs parent in the room to fall asleep
7. Child resists going to bed at bedtime
8. Child sleeps about the same amount each day*
9. Child is restless and moves a lot during sleep
10. Child moves to someone else's bed during the night (parent, brother, sister, etc.)
11. Child snores loudly
12. Child awakens during the night screaming, sweating, and inconsolable
13. Child napes during the day
14. Child awakens once during the night
15. Child awakens more than once during the night
16. Child wakes up very early in the morning
17. Child seems tired during the daytime
18. Child falls asleep while involved in activities

Total Score (18 items)

Scoring: Always = 5 Usually = 4 Sometimes = 3 Rarely = 2 Never = 1

*Items 1, 2, 3 and 8 are reversed in scoring, so that a higher score reflects more disturbed sleep behavior

Table 1

Baseline characteristics of patients with pseudohypoparathyroidism type 1a

	Prospective Study n= 19	Retrospective Study n= 18	P value
Age (years)	10.4 ± 5.2	11.1 ± 5.5	0.69
Race (% Caucasian)	100	94	0.23
Gender (% female)	68	72	1.00
BMI z-score	2.24 ± 0.60 (n= 16)	2.26 ± 0.53 (n= 16)	0.92
Asthma (% affected)	32	50	0.33
Growth hormone (% on treatment)	11	11	1.00
Snoring (% affected)	53	50	1.00
Sleep apnea (% affected)	58	39	0.33

BMI, body mass index. BMI z-scores were calculated as standard deviations from the mean using gender and age specific Centers for Disease Control growth charts. Data expressed as mean ± SD. Continuous variables were compared using Student's t-test. Categorical variables were compared using Fisher's Exact test.

Table 2

Baseline characteristics of all patients in the combined analysis (n= 31)

Age (years)	10.7 ± 5.6
Race % aucasian)	94
Gender (% female)	68
BMI z-score	2.20 ± 0.59 (n= 26)
Asthma (% affected)	39
Growth hormone (% on treatment)	13
Snoring (% affected)	52
Sleep apnea (% affected)	45

BMI, body mass index. BMI z-scores were calculated as standard deviations from the mean using gender and age specific Centers for Disease Control growth charts. Data expressed as mean ± SD.

Table 3

Combined analysis of all patients with and without sleep apnea

	No Sleep Apnea (n=17)	Sleep Apnea (n=14)	P value
Age (years)	12.8 ± 5.0	8.1 ± 5.4	0.02
Gender (% female)	82	50	0.12
Asthma (% affected)	24	57	0.08
Growth hormone (% on treatment)	12	14	1.00
BMI Z-score	2.07 ± 0.14 (n= 15)	2.38 ± 0.65 (n= 11)	0.19

BMI, body mass index. BMI z-scores were calculated as standard deviations from the mean using gender and age specific Centers for Disease Control growth charts. Data expressed as mean ± SD. Continuous variables were compared using Student's t-test. Categorical variables were compared using Fisher's Exact test.