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Enuresis Associated with Sleep Disordered Breathing in Children with Sickle Cell Anemia

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Abstract

Purpose—Enuresis and sleep disordered breathing are common among children with sickle cell anemia. We evaluated whether enuresis is associated with sleep disordered breathing in children with sickle cell anemia.

Materials and Methods—Baseline data were used from a multicenter prospective cohort study of 221 unselected children with sickle cell anemia. A questionnaire was used to evaluate, by parental report during the previous month, the presence of enuresis and its severity. Overnight polysomnography was used to determine the presence of sleep disordered breathing by the number of obstructive apneas and/or hypopneas per hour of sleep. Logistic and ordinal regression models were used to evaluate the association of sleep disordered breathing and enuresis.

Results—The mean age of participants was 10.1 years (median 10.0, range 4 to 19). Enuresis occurred in 38.9% of participants and was significantly associated with an obstructive apnea-hypopnea index of 2 or more per hour after adjusting for age and gender (OR 2.19; 95% CI 1.09, 4.40; $p = 0.03$). Enuresis severity was associated with obstructive apneas and hypopneas with 3% or more desaturation 2 or more times per hour with and without habitual snoring (OR 3.23; 95% CI 1.53, 6.81; $p = 0.001$ and OR 2.07; 95% CI 1.09, 3.92; $p = 0.03$, respectively).

Conclusions—In this unselected group of children with sickle cell anemia, sleep disordered breathing was associated with enuresis. Results of this study support that children with sickle cell anemia who present with enuresis should be evaluated by a pulmonologist for sleep disordered breathing.

Keywords

enuresis; sleep; anemia; sickle cell

ENURESIS is a common and pervasive problem in children with sickle cell anemia, affecting 20% to 69% of children age 5 to 18 years^{1–5} compared to less than 1% to 15% of similar age children in the general population.^{6,7} Furthermore, enuresis persists among young adults with SCA, affecting approximately 9% of individuals older than age 18 years.⁵

Sleep disordered breathing, specifically habitual snoring and obstructive sleep apnea-hypopnea syndrome, has been previously investigated as a risk factor for enuresis in nonSCA children.^{8–14} Although definitions of habitual snoring, obstructive sleep apnea-hypopnea syndrome, enuresis and age ranges have varied, a study of 5 to 14-year-olds (after adjusting for age and gender) demonstrated that enuresis, defined as incontinence while asleep at least 1 night a week, was 3.54 times more prevalent among those with habitual snoring (more than 3 nights per week) than among nonsnorers.⁹ Studies evaluating the association between enuresis and habitual snoring, as a proxy for SDB, among children without SCA have shown that enuresis was more prevalent among snorers than nonsnorers (26.9% vs 11.6%; $p < 0.00001$; OR 2.79; 95% CI 2.50, 3.13).¹⁰ However, the degree of SDB was not associated with the presence of enuresis.

In select case series of children with SCA referred for polysomnography due to clinical symptoms of SDB and/or abnormal pulse oximetry, prevalence of SDB was 35% to 79%.^{15,16} To date, these findings have not been confirmed in an unselected group of children with SCA. To our knowledge no association between enuresis and SDB in sickle cell anemia, diagnosed using polysomnography, has been analyzed in detail. However, a recent study using the CSHQ (Children's Sleep Habits Questionnaire) suggests that symptomatic sleep disordered breathing is significantly correlated with enuresis in children with SCA.¹⁷ We tested the hypothesis that the prevalence and severity of enuresis are associated with SDB in children with sickle cell anemia who are not specifically selected due to suspicion of SDB.

MATERIALS AND METHODS

Study Design

The SAC (Sickle Cell Anemia Sleep and Asthma Cohort) study (1R01HL079937-01), approved by the institutional review board at Washington University School of Medicine, Case Western Reserve and United Kingdom National Research Ethics Service, is a multicenter cohort study designed to assess asthma and nocturnal oxygen desaturation episodes in children with SCA. Baseline information included physical examination, CSHQ and overnight PSG.

SAC participants were recruited from pediatric hematology clinics in St. Louis, Missouri; Cleveland, Ohio and London, England from June 1, 2006 through December 31, 2009. Eligible children were between 4 to 18 years old at enrollment, regularly followed in a hematology clinic, and with parental consent. Children were excluded from study if diagnosed with HIV infection, chronic lung disease, heart disease or conditions predisposing them to SDB. Exclusion criteria were having received chronic blood transfusion therapy; participation in clinical trials involving blood transfusions, oxygen or hydroxyurea interventions and those deemed noncompliant by the hematologist or pediatrician.

Polysomnography

All sites used identical sleep acquisition systems (Embla N-4000, Broomfield, Colorado) and sensors. Data collection procedures followed current standards for PSG in children with the exclusion of carbon dioxide measurements.¹⁸ Sleep channel measurements included pulse oximetry with recordings of numeric and plethysmograph waveforms using a 2-second averaging mode (Masimo Radical®), airflow by oronasal thermocouple and nasal cannula

(Pro-Tech Services, Mukilteo, Washington), heart rate by electrocardiography channel with a modified 3-lead precordial placement, chest and abdominal wall activity measured by inductive plethysmography with noncalibrated sum signal, leg movements by electromyography, snoring by microphone (Dymedix), and body position using mercury gauge. PSG was performed during a single night with studies commencing at the child's usual bedtime and ending at spontaneous waking or as late as 7:00 am.

Definitions

Enuresis history was assessed on the night of PSG using a modified CSHQ.¹⁹ Parents answered "How many times did the child wet the bed in the previous month?" Enuresis was defined as at least 1 bedwetting episode in the last month. Severity was described as no enuresis episodes, mild (less than 3 episodes weekly) or severe (3 or more episodes per week). We chose this grouping a priori because it was believed that parents would be able to accurately recollect and distinguish among no, mild and severe enuresis. Habitual snoring was also assessed using the sleep questionnaire by response to, "How many times did your child snore in the previous month?" Habitual snoring was defined dichotomously as those who reported snoring 3 or more nights per week.

SDB was defined as the occurrence of 2 or more events per hour of obstructive apneas (including mixed apneas) or hypopneas with 3% or more oxygen desaturation ($\text{OAHI}_3 \geq 2$). Central apneas were not included. Respiratory event scoring was based on the American Academy of Sleep Medicine Manual for scoring obstructive respiratory events in children with minor modifications.¹⁸ Hypopneas were defined as decreases in nasal pressure or oronasal flow of at least 50% associated with a corresponding decrease in arterial oxygen saturation of 3% or more from baseline. If a direct airflow signal was not available, then hypopneas were defined as a 50% reduction of the sum signal from the respiratory inductance plethysmography bands associated with a desaturation.²⁰ Hypopneas associated only with arousals were not scored. Children with $\text{OAHI}_3 \geq 2$ were further characterized in terms of the presence or absence of habitual snoring.

Statistical Analysis

Means and standard deviations were computed for continuous variables. Frequencies and percentages were computed for categorical variables. One-way ANOVA and chi-square tests were conducted for continuous and categorical covariates, respectively. The Kruskal-Wallis test was used for OAHI_3 as this variable was positively skewed. Covariates included age, gender, history of adenotonsillectomy, study center and BMI based on gender, ethnicity and age percentile according to Centers for Disease Control and Prevention growth charts.²¹

Logistic regression analysis, with the dependent variable being the presence or absence of enuresis, was used to examine whether habitual snoring and SDB were risk factors for at least 1 episode of enuresis in the last month. Assumptions including absence of multicollinearity were met. Backwards elimination modeling assessed for effect modification and confounding of potential covariates. Potential confounders included age, gender, BMI percentile, history of adenoidectomy or tonsillectomy, use of hydroxyurea in the last 3 years, and history of asthma diagnosis. Potential effect modification due to gender and center was evaluated using respective interaction terms in the model. Potential covariates were assessed using a Wald chi-square test at a significance level of $\alpha = 0.1$ and statistically significant covariates were included in the final model. Logistic regression analysis was repeated, defining enuresis as severe (3 or more episodes per week in the last month).

After the association of enuresis and SDB was evaluated, ordinal regression analysis was used to determine if enuresis severity (no enuresis, mild and severe) was associated with habitual snoring and SDB. Three ordinal regression models were used to examine whether 1) habitual snoring, 2) SDB without habitual snoring and 3) SDB with habitual snoring were significant risk factors for the frequency of enuresis. The parallel lines assumption was met for all models, that is habitual snoring ($p = 0.12$), SDB without habitual snoring ($p = 0.13$) and SDB with habitual snoring ($p = 0.06$). The proportional odds assumption was met with a score test for each model ($p > 0.05$). Model fit was evaluated using the likelihood ratio test ($p < 0.01$). A backwards elimination method with predictors entered with $p < 0.1$ assessed for effect modification and confounding effects as previously stated. The ordinal regression models were then used to provide crude and adjusted OR and corresponding 95% CI. Data were analyzed using PASW® Statistics 18.0 and SAS® 9.2.

RESULTS

Demographics and Patient Characteristics

A total of 424 children were approached to participate in this prospective observational study, of whom 146 declined. Of the 264 patients who consented/assented to participate, 18 children had hemoglobin SC and were excluded from this analysis. Of the 246 enrolled participants, 25 were excluded due to an unacceptable PSG study (17) or lack of response from caregivers regarding bedwetting or snoring (8). A total of 221 children had a confirmed diagnosis of hemoglobin SS or beta thalassemia (hemoglobin S β), and completed the sleep questionnaire and a PSG of acceptable quality. Compared to children excluded from the analysis (25), participants were not significantly different in age, gender, BMI percentile, history of adenotonsillectomy, habitual snoring and SDB. Mean age of the study cohort was 10.1 ± 4.2 years (median 10.0, range 4 to 19) with 49.3% male (table 1). Average BMI percentile was $50.1\% \pm 29.9\%$ (median 49.6, IQR 51.5). In the cohort 16.3% had previously undergone adenotonsillectomy due to a previous diagnosis of SDB.

Prevalence of Enuresis, Habitual Snoring and SDB

Enuresis was common with 38.9% of participants having at least 1 bedwetting episode in the month before PSG, occurring in 56.4% of 4 to 6-year-olds (31 of 55), 63.0% of 7 to 9-year-olds (29 of 46) and 21.7% of children at least 10 years old (26 of 120). Among the participants 15.3% (34) had mild enuresis and 23.6% (52) had severe enuresis (table 1). OAH_{I3} 2 with and without habitual snoring, and habitual snoring alone, were also common, occurring in 15.4%, 23.5% and 33.5% of participants, respectively. Among habitual snorers 34.7% had enuresis while 33.7% of children without SDB (with and without habitual snoring) had enuresis.

Age and gender were significantly different among children with mild, severe, or no enuresis ($p < 0.001$). Compared to children without enuresis those with severe enuresis were younger and a greater proportion was male. BMI percentile (OR 1.0; 95% CI 0.99, 1.01; $p = 0.91$), previous adenoidectomy or tonsillectomy (OR 0.55; 95% CI 0.25, 1.21; $p = 0.14$), use of hydroxyurea in the last 3 years (OR 0.36; 95% CI 0.07, 1.74; $p = 0.20$) and asthma diagnosis (OR 1.12; 95% CI 0.64, 1.94; $p = 0.70$) did not differ significantly among children with severe, mild or no enuresis. Approximately a third of children (38.5%, 20 of 52) with severe enuresis had OAH_{I3} 2. Interestingly more than a third (34.6%, 18 of 52) of children with SDB were not reported as habitual snorers.

Enuresis Associated with SDB

After adjusting for age and gender, the presence of enuresis was associated with OAH_{I3} 2 (OR 2.19; 95% CI 1.09, 4.40; $p = 0.03$, table 2). A similar association with OAH_{I3} 2 was

noted in crude and adjusted models among those with severe enuresis, defined as 3 or more episodes weekly in the last month (adjusted OR 2.26; 95% CI 1.09, 4.70; $p = 0.03$).

In 3 separate ordinal regression models enuresis severity (no enuresis, mild and severe) was significantly associated with 1) habitual snoring, 2) OAH₃ - 2 without habitual snoring and 3) OAH₃ - 2 with habitual snoring (table 3). The association of habitual snoring alone and severe enuresis among children with SCA was statistically significant after adjusting for age and gender (OR 1.83; 95% CI 1.02, 3.29; $p = 0.043$). Similarly for children with OAH₃ - 2 with and without habitual snoring, the adjusted ORs of severe enuresis were significant (OR 3.23; 95% CI 1.53, 6.81; $p = 0.002$ and OR 2.07; 95% CI 1.09, 3.92; $p = 0.025$, respectively).

DISCUSSION

Among children with SCA, enuresis is common, and a cause for significant psychosocial problems and decreased quality of life.^{4,22} In SCA polyuria due to renal concentrating defects likely contributes to the high rate of enuresis, but other factors may also be important. Our data provide support for the hypotheses that the prevalence as well as the severity of enuresis are associated with sleep disordered breathing in children with SCA.

This study demonstrates that habitual snoring and SDB with and without habitual snoring are associated with enuresis in children with SCA, consistent with the findings of studies conducted in the general pediatric population.^{10,11,14} In this study the prevalence of enuresis in children with SCA without sleep disordered breathing was higher than that in the general pediatric population. Future studies can be done to evaluate whether children with SCA without sleep disordered breathing are at increased risk for enuresis compared to historical controls.

To our knowledge this is the first cross-sectional study of an unselected cohort of children with SCA who were evaluated for snoring, SDB with and without snoring, and enuresis. Although a history of habitual snoring may alert to the possibility that a child with SCA and enuresis may have SDB as a potentially modifiable cause, a substantial proportion of children with SCA and enuresis in this cohort had SDB without habitual snoring. Thus, an important research priority is to determine whether SDB without habitual snoring is a modifiable cause of enuresis in those with and without SCA.

For children with SCA and enuresis the results of this study should prompt clinicians to increase surveillance for SDB. In a school-age child with SCA, enuresis and a history of snoring, one must strongly consider a more formal assessment by a sleep specialist or pulmonologist. If SDB is found and the child has significant adenotonsillar hypertrophy, then adenotonsillectomy would be the next line of therapy.²³ Previous studies in the general pediatric population have shown reduction of enuresis after adenotonsillectomy.^{24,25} Although history of adenotonsillectomy did not appear to significantly reduce enuresis in this cohort, the sample size was small and point estimates had wide confidence intervals. There is controversy regarding whether this surgery is an efficacious treatment for enuresis as a recent prospective controlled study found no association between tonsillar hypertrophy and urinary incontinence before or any change in enuresis after tonsillectomy.²⁶ Further studies evaluating the effect of medical and surgical management strategies for SDB on enuresis, in parallel with the effect on PSG, are warranted.²⁷

This study had limitations. We did not perform a formal analysis differentiating patients with primary and secondary enuresis (previously dry period of at least 6 months), although a majority of children with SCA are expected to have secondary enuresis. This study also did not differentiate between monosymptomatic and nonmonosymptomatic enuresis (enuresis

with lower urinary tract dysfunction). Despite being the largest study of an unselected cohort of children with sickle cell anemia who underwent PSG, our sample size precluded a meaningful sub-group analysis (ie children older than 5 years) as it was not planned a priori and the primary hypothesis of this study was to evaluate whether enuresis was associated with SDB. Further exploration is warranted to determine whether high risk groups can be identified with a stronger association between enuresis and SDB, which would facilitate the identification of those requiring PSG. Another limitation in this study was the use of cross-sectional analyses of the SAC study cohort rather than longitudinal analysis, limiting strong inferences about causality. Despite these limitations, the patterns of association between enuresis and habitual snoring as well as SDB with and without habitual snoring were consistent.

CONCLUSIONS

In summary, we have provided evidence that a child with SCA who manifests with enuresis should be considered at significant risk for SDB even in the absence of habitual snoring. Further research is needed to confirm this association and to explore targeted treatment options specific to sleep disordered breathing to decrease enuresis in children with SCA.

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Abbreviations and Acronyms

BMI	body mass index
OAHI₃	obstructive apnea-hypopnea index at 3% desaturation
OAHI₃ 2	obstructive apneas and hypopneas with 3% or more desaturation 2 or more times per hour
PSG	polysomnography
SCA	sickle cell anemia
SDB	sleep disordered breathing

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Table 1

Demographic and clinical characteristics

	All Participants	No Enuresis	Mild Enuresis	Severe Enuresis	p Value
No. pts (%)		135 (61.1)	34 (15.3)	52 (23.6)	
Mean pt age (SD)	10.1 (4.2)	11.4 (4.2)	8.2 (3.7)	8.2 (3.4)	<0.001
Mean BMI percentile (SD)	50.1 (29.9)	50.3 (29.8)	45.9 (30.3)	52.4 (29.9)	0.623
No. male gender (%)	109 (49.3)	56 (41.5)	15 (44.1)	38 (73.1)	<0.001
No. previous adenoidectomy or tonsillectomy (%)	36 (16.3)	26 (19.3)	5 (14.7)	5 (9.6)	0.268
No. use of hydroxyurea (%)	10 (5.0)	8 (6.7)	1 (3.1)	1 (2.1)	0.400
No. asthma (%)	86 (39.1)	51 (38.1)	10 (29.4)	25 (48.1)	0.206
No. habitual snoring (%)	74 (33.5)	39 (28.9)	11 (32.4)	24 (46.2)	0.080
No. SDB without habitual snoring (%)	52 (23.5)	23 (17.0)	9 (26.5)	20 (38.5)	0.008
No. SDB with habitual snoring (%)	34 (15.4)	12 (8.9)	5 (14.7)	17 (32.7)	<0.001

Table 2

Multivariable logistic regression describing association of SDB and enuresis

	SDB Crude OR (95% CI)	SDB Adjusted OR (95% CI)
Enuresis 1+ nights/wk	2.48 (1.32, 4.67)	2.19 (1.09, 4.40)
Enuresis 3+ nights/wk	2.68 (1.36, 5.27)	2.26 (1.09, 4.70)

Table 3

Evaluation of habitual snoring, and SDB with and without habitual snoring as risk factors for severe enuresis

	Crude OR (95% CI)	Adjusted OR (95% CI)
Habitual snoring 3+ nights/wk	1.79 (1.04, 3.11)	1.83 (1.02, 3.29)
SDB without habitual snoring	2.55 (1.40, 4.65)	2.07 (1.09, 3.92)
SDB with habitual snoring	3.93 (1.94, 7.95)	3.23 (1.53, 6.81)