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

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Abbreviations and Acronyms

BMI = body mass index

$OAHI_3$ = obstructive apnea-hypopnea index at 3% desaturation

$OAHI_3 \geq 2$ = 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

Study received institutional review board approval.

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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.

Key Words: 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

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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 ($OAHI_3 \geq 2$). 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 $OAHI_3 \geq 2$ 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