Wheezing Symptoms and Parental Asthma Are Associated with a Physician Diagnosis of Asthma in Children with Sickle Cell Anemia

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Objective To identify factors associated with asthma associated with increased sickle cell anemia (SCA).
Study design Children with SCA (N = 187; mean age 9.6 years, 48% male) were classified as having "asthma" based on parent report of physician diagnosis plus prescription of asthma medication (n = 53) or "no asthma" based on the absence of these features (n = 134). Pain and acute chest syndrome (ACS) events were collected prospectively.
Results Multiple variable logistic regression model identified 3 factors associated with asthma: parent with asthma (P = .006), wheezing causing shortness of breath (P = .001), and wheezing after exercise (P < .001). When ≥2 features were present, model sensitivity was 100%. When none of the features were present, model sensitivity was 0%. When only 1 feature was present, model sensitivity was also 0%, and presence of ≥2 of positive allergy skin tests, airway obstruction on spirometry, and bronchodilator responsiveness did not improve clinical utility. ACS incident rates were significantly higher in individuals with asthma than in those without asthma (incident rate ratio 2.21, CI 1.31-3.76), but pain rates were not (incident rate ratio 1.28, CI 0.78-2.10).
Conclusions For children with SCA, having a parent with asthma and specific wheezing symptoms are the best features to distinguish those with and without parent report of a physician diagnosis of asthma and to identify those at higher risk for ACS events. The value of treatment for asthma in the prevention of SCA morbidity needs to be studied. *(J Pediatr 2014;164:821-6)*.

Asthma in a child with sickle cell anemia (SCA) is associated with an increased rate of pain and acute chest syndrome (ACS)[1-8] and premature death.[9] Thus, determining the clinical symptoms and historical and laboratory features associated with a physician diagnosis of asthma within the context of SCA would be important to identify patients at increased risk for complications. Reports that have demonstrated the association between a physician diagnosis of asthma and increased morbidity in children with SCA have not provided details of symptoms or other clinical factors that were associated with a physician's diagnosis of asthma.

Our primary objective was to determine whether clinical and laboratory features could distinguish children with SCA and a physician diagnosis of asthma from children with SCA without such a diagnosis. We used data from the Sleep and Asthma Cohort study, a multicenter prospective cohort focused on assessing the long term-complications of asthma and sleep disordered breathing in children with SCA sponsored by the National Heart, Lung, and Blood Institute (NHLBI). We tested the hypothesis that among children with SCA, respiratory symptoms, parental history of asthma, evidence of atopy (elevated levels of total serum IgE and peripheral blood eosinophil counts and positive results of epicutaneous skin tests to aeroallergens), and presence of bronchodilator responsiveness and/or evidence of airway obstruction would be associated with a parent report of a physician's diagnosis of asthma and prescription of antiasthma therapy. We also examined the impact of asthma on rates of pain and ACS episodes collected prospectively over almost 5 years of follow-up.

Methods

The current study uses data collected at baseline and prospectively as part of our observational cohort study of children with SCA, either hemoglobin SS or

ACS	Acute chest syndrome
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
IRR	Incident rate ratio
LLN	Lower limit of normal
NHLBI	National Heart, Lung, and Blood Institute
SCA	Sickle cell anemia
WBC	White blood cell

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sickle-β°-thalassemia, enrolled from 4 to 18 years of age (mean 9.6) at 3 clinical centers and followed for 4.61 ± 1.16 years. Children were enrolled without regard to past morbidity or physician diagnosis of asthma, but those on long-term transfusion or participating in a clinical trial evaluating hydroxyurea therapy were not eligible. Institutional approval was obtained from participating sites—Washington University School of Medicine in St Louis, Missouri; Case Western Reserve University in Cleveland, Ohio; and University College London in London, UK (which recruited from 3 London hospitals)—and from the Coordinating Center at Vanderbilt School of Medicine in Nashville, Tennessee. Informed written parental consent was obtained, and children were consented or assented on enrollment according to institutional policies of each institution.

During initial interviews, parents were asked if a physician had ever diagnosed their child as having asthma, what medications their child was currently receiving (using a list that included asthma relievers [eg, albuterol] and controllers [eg, inhaled corticosteroid and leukotriene modifier]) and to complete the American Thoracic Society/Division of Lung Diseases questionnaire[10] regardless of asthma status. Spirometry before and after bronchodilator (4 inhalations of albuterol, 90 μg/inhalation, via a valved holding chamber), allergy skin tests using the prick puncture technique with the multitest (Lincoln Diagnostics, Decatur, Illinois) to 9 aeroallergens (*Aspergillus* and *Alternaria* molds, cat, dog, dust mite, cockroach, and site-specific tree, grass, and weed pollens), and methacholine challenges were performed as previously reported.[11-13] Total serum IgE and a complete blood count with determination of white blood cell (WBC) count and percentage of eosinophils were performed using standard techniques in each clinical center.

Definitions of Vaso-occlusive Pain Episode and ACS

A vaso-occlusive pain episode was defined as bone pain in chest, extremities, or other areas (not headaches only) directly associated with SCA that required hospitalization for treatment with opioids. ACS was defined as an episode of acute respiratory distress with at least a new radiodensity on chest roentgenogram, temperature >38°C, and increased respiratory effort, with a decrease in oxygen saturation or increased respiratory rate documented in the medical record. To ensure a uniform definition of pain and ACS in this multicenter study, all ACS and vaso-occlusive pain episodes requiring hospitalization were reviewed by a single investigator at each participating site, with overreading by the principal investigator (M.D.). Concerns about the assignment of the diagnosis raised by the principal investigator were discussed with the site investigators, and consensus was reached.

Classifications as Asthma and Nonasthma

Two hundred fifty-two subjects were enrolled with a diagnosis of SCA, 95% with hemoglobin SS and 5% with sickle-β°-thalassemia (**Figure**). Subjects were classified as having asthma, based on a physician diagnosis of asthma and current prescription of an asthma medication, or as no asthma, based on having neither a physician diagnosis of asthma nor an asthma medication (**Figure**).

Participants did not meet our criteria for "asthma" if they either had a physician diagnosis but no asthma medication (n = 15) or albuterol prescribed without a physician diagnosis (n = 10). These participants were not included in the analysis so as to have the classifications of asthma and nonasthma discrete for purposes of understanding the characteristics of asthma among children with SCA.

Of the 227 subjects with an asthma classification, 40 had missing data on at least 1 of the 8 covariates in the model (**Figure**). Rates of missing data for each group ranged from 0.4% for wheeze causing shortness of breath, wheeze without colds, wheeze with colds, and wheeze after exercise, to 0.9% for cough without colds and phlegm without colds, to 3.1% for whether mother has asthma, to 14.5% for whether either parent has asthma and 15.4% for whether father has asthma. These 40 subjects were not included in the initial logistic regressions to maintain a consistent case basis for the models; a process of data imputation was not used because there were no other variables that would reliably predict maternal and paternal asthma. An analysis of the differences between subjects with and without missing data showed no large or consistent differences.

Statistical Analyses

All data from subjects in the asthma and no asthma study groups were combined and continuous variables were assessed for normality. Analyses were conducted using Stata statistical software (StataCorp LP, Version 12, College Station, Texas) and IBM SPSS Statistics (IBM, Version 20, Chicago, Illinois). Continuous data that were normally distributed were analyzed using *t*-tests, skewed data were analyzed with the Mann–Whitney–Wilcoxon test, and categorical data were analyzed using χ^2 tests. Variance is reported using SDs or IQRs.

A multivariable logistic regression was performed using characteristics postulated to be relevant to a diagnosis of asthma that could be readily available to a clinician conducting an initial interview using the American Thoracic Society/Division of Lung Diseases questionnaire with a patient and family: wheeze, cough, and phlegm production without colds; wheeze after exercise; wheeze causing shortness of breath; and either mother and father with asthma or either parent with asthma. Due to collinearity between mother and father with asthma, each had to be assessed separately. Because both allergy skin test results and spirometry variables of bronchodilator response and the ratio of the percentage of those with an forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) below the lower limit of normal (LLN) were significantly different between the asthma and no asthma groups, these variables were used subsequently to determine if they added any explanatory power to the results of the logistic regression analyses. Relationships between asthma diagnosis and prospective rates of pain and ACS