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Sibling History of Asthma is a Risk Factor for Pain in Children with Sickle Cell Anemia

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Abstract

The basis of the association between asthma and an increased rate of pain among children with sickle cell anemia (SCA) is unclear. To provide evidence for a familial contribution to this observation, we tested the hypothesis that a family history of asthma is associated with an increased pain rate. Using data from the Cooperative Study for Sickle Cell Disease (CSSCD), we identified 211 children with SCA with asthma history of the parents and siblings. A sibling history of asthma was associated with a greater rate of pain (mean rate ratio = 2.48, 95% CI 1.6–4.0; $p < 0.001$) when compared to children without a sibling history of asthma. Parental history of asthma was not associated an increase rate of pain (mean ratio = 1.51, 95% CI 0.92 to 2.62; $P = 0.12$). Further studies are needed to examine genetic and/or environmental risks for asthma as potential contributors to pain in children with SCA.

Keywords

Sickle cell disease; asthma; pain; acute chest syndrome

Introduction

Children with HbSS, referred to as sickle cell anemia (SCA), have significant phenotypic heterogeneity. Variation in disease severity among individuals with SCA is likely due to genetic and/or environmental factors which interact with the SCA mutation(1). Among children with SCA, a diagnosis of asthma is associated with an increased incidence of pain(2,3). Similar to SCA, asthma is a heterogeneous disorder, and asthma susceptibility results from complex gene-environment interactions(4). Given that asthma and SCA are distinct co-morbid conditions(5) and that asthma is associated with more frequent painful episodes, we postulate that familial risks for asthma (genetic or environmental) may be important modifiers for disease severity among individuals with SCA. To provide evidence

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that asthma-related familial factors increase the rate of painful episodes, we examined a cohort of infants who were part of the Cooperative Study for Sickle Cell Disease (CSSCD). Many children in this cohort were included in a previous study by our group demonstrating that a diagnosis of asthma is associated with an increased rate of pain and acute chest syndrome (ACS)(3). We tested the hypothesis that a family history of asthma is associated with a higher rate of pain in children with SCA.

Results

Our cohort consisted of 211 African-American children with SCA. Fifty-one percent of the cohort was male. The mean age of study entry was four months and the cohort was followed for a mean of 9.6 years. In the cohort, 14% (30 of 211) reported a sibling history of asthma, 12% (26 of 211) reported a parental history of asthma, and 22% (47 of 211) reported a history of asthma in either siblings or parents. Twenty percent (42 of 211) had a diagnosis of asthma. Of those children with a family history of asthma in either siblings or parents, 47% (22 of 47) also had a diagnosis of asthma (odds ratio 6.4, 95% CI 2.8 to 14.1, $p < .001$). The mean age that asthma was reported was 9.5 years.

A history of asthma among siblings was associated with an increase in SCA-related morbidity (Table I). The adjusted rate of pain episodes in children with a sibling history of asthma was 1.41 episodes per year versus 0.57 episodes per year in children without a sibling history of asthma (mean rate ratio= 2.48, 95% CI 1.60–4.00, $P < 0.001$). Sibling history of asthma was also associated with an increased rate of ACS episodes. The adjusted rate of ACS episodes in children with a sibling history of asthma was 0.41 episodes per year compared to 0.22 episodes per year in children without a family history of asthma (mean rate ratio= 1.86, 95% CI 1.23–2.89, $P = 0.004$). Parental history of asthma was not associated with significantly increased rates of pain or ACS episodes after controlling for previously identified risk factors (pain: mean ratio = 1.51, 95% CI 0.92 to 2.62, $P = 0.12$; ACS mean ratio = 1.29, 95% CI 0.81 to 2.11, $P = 0.30$).

We evaluated whether sibling history of asthma served only as a proxy for the correlated risk of a patient themselves having asthma or whether sibling history was an independent risk factor by including both terms in our analysis. Note that rates of pain and ACS episodes did not depend on interactions between personal and sibling histories of asthma ($P > 0.45$). The independent association between sibling history of asthma and pain after controlling for personal history of asthma was still significant and ACS was nearly so (pain: mean ratio = 1.91, 95% CI 1.18 to 3.09, $P = 0.008$; ACS mean ratio = 1.48, 95% CI 0.97 to 2.26, $P = 0.07$).

Discussion

Prior to this study, the influence of a family history of asthma on SCA-related morbidity was not defined. Our group has previously established that physician diagnosis of asthma is associated with greater SCA-related morbidity(2,3,6,7); however, the mechanism for this association was unclear. We postulated that the disease-modifying effects of asthma were due in part to familial factors related to asthma. These results provide support for that hypothesis, namely that children with SCA and a sibling history of asthma had a clinically relevant and statistically significant increase in the incidence rate of pain episodes. Our study could not determine whether genetic or environmental causes of asthma were responsible for the observed association between sibling history of asthma and increased pain. Although parental history of asthma would have provided the strongest evidence for a genetic influence on the severity of SCA, our results do not exclude a significant genetic contribution to the disease-modifying affect of asthma. The adjusted rates of pain and ACS among children with parental history of asthma, while not statistically significant, suggest

increased morbidity. Parental asthma histories are typically remote and may not be as accurate as sibling histories(8). Further, sibling history of asthma has been demonstrated to be a strong independent predictor of asthma(9).

Limitations are present in this study. In the CSSCD, family history of asthma was self-reported, and study participants may not have been knowledgeable about asthma diagnoses within their family. However, under-reporting of asthma family history, the most likely type of bias, would bias our results toward the null hypothesis. Although our study has limitations, these results are consistent with our previous finding that asthma is associated with an increased rate of pain(2,3). Based on the findings in this study and others implicating the role of asthma in SCA-related morbidity, we believe that further studies are required to identify specific genetic or environmental factors related to asthma that may be involved in modifying SCA morbidity.

Methods

Patient Population

The CSSCD study design has previously been reported(10). Human subject committee approval was obtained at participating sites, and participants were consented prior to study entry. We obtained additional institutional review board approval to analyze the CSSCD data held by the National Heart, Lung, and Blood Institute.

For inclusion in this cohort, we identified African-American infants with hemoglobin SS, enrolled in the CSSCD study prior to age 6 months, followed past the age of 5 years and for whom asthma family history data was collected. Participants who had insufficient clinical data or did not have a sibling were excluded from this cohort (Figure 1). The follow-up period for pain and ACS started upon study enrollment and ended when any of the following events occurred: last required routine CSSCD visit, transfer to a non-CSSCD clinic, initiation of chronic blood transfusion therapy or hydroxyurea, a cerebrovascular event, bone marrow transplantation or death(3).

Definitions

Painful episode—A painful episode was defined as per CSSCD protocol, as pain in the extremities, back, abdomen, chest, or head for which no explanation other than SCA could be found, lasting at least 2 hours, and leading to a clinic visit (3,11).

ACS—ACS episodes were defined as per CSSCD protocol as a new pulmonary infiltrate demonstrable on chest radiograph or perfusion lung scan, or pleuritic chest pain with an abnormal perfusion scan (12,13).

Asthma—Asthma was defined for children older than 5 years of age as those who had a clinical diagnosis of asthma recorded during any annual study visit after 5 years of age, who presented with acute asthma event (determined by ICD-9 codes, 493.xx) during the study period, or who had use of asthma medications (generally bronchodilators) reported on the clinic visit form. Parent report of a clinical diagnosis of asthma was assessed on a history form and also on a pulmonary intake form at the time of pulmonary function testing. The question, “Does the patient currently carry a diagnosis of asthma?” was asked annually(3).

Family History of Asthma—Parental or sibling history of asthma was defined as any report of a history of asthma among parents or siblings, respectively, from annual interviews which asked, “Have any of the following members of the child’s family [separate entries for:

Mother, Father, Sister, Brother] ever had asthma?” Although it may be environmentally induced, an assumption was made that asthma is a life-long illness.

Outcome Measures and Statistical Methods

Data analysis was performed in SAS, version 9.1. Incidence rates of pain and ACS episodes were estimated using generalized linear models assuming that counts of events followed a negative binomial distribution with scale parameter estimated by maximum likelihood and a log link function. In addition to classification of family history of asthma, the models included the following covariates: a) ACS rate: age at end of follow-up and lifetime average hemoglobin concentration, white blood cell count, and percent fetal hemoglobin(12), and b) pain episode rate: age at end of follow-up, gender, and lifetime average hematocrit and percent fetal hemoglobin(11). Additional analysis included a personal history of asthma as another covariate. Laboratory values (lifetime average hemoglobin, white blood cell count, and percent fetal hemoglobin) were determined based on the average of all values during follow-up, excluding laboratory values during events and percent fetal hemoglobin before 2 years of age.

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Figure 1.
Establishing a sickle cell anemia infant cohort from the Cooperative Study for Sickle Cell Disease

Table I

Mean rate ratio for pain episodes in children with SCA with and without sibling and parental history of asthma

Characteristic	Mean rate ratio for pain episodes	95% CI	P value
Without adjustment for personal asthma			
Sibling asthma	2.48	1.60–4.00	<0.001
Parental asthma	1.51	0.92–2.62	0.120
With adjustment for personal asthma			
Sibling asthma	1.91	1.18–3.09	0.008
Parental asthma	1.12	0.65–1.91	0.682

CI= Confidence interval