Application of an Asthma Screening Questionnaire in Children with Sickle Cell Disease

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Objective: Asthma in sickle cell disease (SCD) patients is associated with elevated morbidity and mortality. Early detection and initiation of treatment may therefore lead to improved outcome. Utility of an asthma screening questionnaire to identify obstructive airway disease and physician diagnosed asthma in children with SCD at an outpatient setting as an effective, easy-to-administer screening tool has not previously been evaluated in this population.

Methods: A previously validated asthma screening questionnaire and spirometry were prospectively administered to 41 SCD children at a routine clinic visit.

Results: Prevalence of obstructive airway was 51.2% ($n = 21$) and physician diagnosis of asthma 33.3% ($n = 13$). Sensitivity (40%) and specificity (75%) of the questionnaire was poor in detecting obstructive airway disease, but sensitivity (77%), specificity (100%), positive predictive value (100%), and negative predictive value (90%) were high in detecting physician diagnosis of asthma.

Conclusion: An asthma screening questionnaire could be a useful tool in identifying at-risk SCD children who may benefit from further management.

Introduction

SICKLE CELL DISEASE (SCD) is the most common hematological genetic disorder disproportionately affecting African Americans. Early identification and treatment of asthma is desirable in this population due to associated increased morbidity¹⁻⁴ and mortality.^{2,5}

Asthma is a heterogeneous chronic airway disease characterized by airway hyper-responsiveness and recurrent episodes of airway obstruction secondary to airway inflammation.⁶ A physician diagnosis of asthma in the general population is largely based on clinical assessment supported by pulmonary function testing or laboratory evidence, which is challenging in SCD due to concurrent wheezing,⁷ respiratory complications such as pneumonia or acute chest syndrome, airway hyper-responsiveness,⁸ and airway obstruction,⁹ attributed to SCD-related airway inflammation but not necessarily a result of asthma. Based on difficulties with diagnosing asthma in SCD children, most studies to date have relied on subjective physician diagnosis, while other series include supporting objective features such as presence of atopy.¹⁰ Poor understanding of the asthma phenotype and definition within this population has

further lead to knowledge gap on early asthma detection and preventive strategies.

Office procedures such as spirometry, methacholine challenge, or exhaled nitric oxide measurement, while helpful in detection of asthma in the general population, have limitations in SCD.^{8,9,11,12} Recently, it was reported that a parental history of asthma and wheezing symptoms were more reliable predictors of physician diagnosed asthma in SCD children compared to spirometry or allergy testing.¹³ Therefore, an asthma screening questionnaire could be a useful tool for identifying at-risk SCD children who warrant further evaluation in the clinic setting. Advantages of an asthma screening questionnaire include the noninvasive nature of the test, cost-effectiveness, easy administration, and fast in-office analysis.

The primary objective of this study was to evaluate the utility of a validated questionnaire¹⁴ to screen for asthma in SCD children in an outpatient setting. Clinical, laboratory data and pulmonary function test of these patients were also assessed, which could potentially distinguish SCD children with obstructive airway impairment or physician diagnosis of asthma from those without, respectively.

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Materials and Methods

Study population

All patients attending the hematology clinic during a routine visit with a diagnosis of SCD, either hemoglobin SS (Hb SS) or sickle- β -thalassemia null (Hb S β^0), between the ages of 5 and 18 years from December 2012 to December 2013 were prospectively invited to take part in this study. Patients were screened for asthma using a validated asthma screening questionnaire and spirometry. Hematological data, including hemoglobin, hematocrit, mean corpuscular volume (MCV), reticulocyte, white blood cell (WBC), neutrophil count, neutrophil percentage, lymphocyte count, lymphocytes percentage, eosinophil count, eosinophil percentage, and platelet count, were obtained at the same clinic visit. One patient did not have hematological testing. Only patients completing both an asthma screening questionnaire and spirometry were evaluated for a physician diagnosis of asthma and included in the data analysis. The study was approved by the Institutional Review Board.

Asthma screening questionnaire

A validated asthma screening questionnaire,^{14,15} consisting of seven questions in English or Spanish, was administered by the hematology clinic nurse. Questions with no response were not analyzed. A positive score on the asthma screening questionnaire was based on a previously described complete algorithm termed Models A to G involving various combinations of four or five question elements,¹⁴ and a three question abbreviated algorithm¹⁵ with a “yes” to question 1 (asthma) or positive responses to both question 4 (exercise related respiratory symptoms) and question 6 (daytime respiratory symptoms). A positive score on the abbreviated algorithm is particularly sensitive and specific in detecting subjects with the highest risk for persistent asthma, based on NIH Guidelines for the Evaluation and Treatment of Asthma. In addition, three specific questions regarding atopic risk were added to the questionnaire (see Supplementary Appendix S1; Supplementary Data are available online at www.liebertpub.com/ped): “Does either of the child’s parents have asthma?” “Has a doctor or nurse diagnosed the child as having allergies?” and “Has a doctor or nurse diagnosed your child as having eczema?”

Classifications of obstructive airway and nonobstructive airway

All recruited patients underwent spirometry (Breeze Suite™ 6.4; Medical Graphics Corporation, St. Paul, MN) as per American Thoracic Society guidelines¹⁶ at the same clinic visit. Traces not meeting quality and reproducibility criteria were excluded.^{16,17} Predicted normative values were based on Knudson revised published data.¹⁸ Spirometry results including forced expiratory volume in 1 sec (FEV₁)/forced vital capacity (FVC) <80% of predicted fixed lower limit of normal, concave shape of the flow-volume loop, flow-time curve, and FEF_{25–75%} were interpreted based on established guidelines¹⁹ independently by two pediatric pulmonologists who were blinded to the asthma screening questionnaire and clinical data as having presence of an obstructive airflow pattern or not. Interpretations were in concordance with each other, except for a study that was independently reviewed by a third pediatric pulmonologist.

The manoeuvre with the largest sum of FEV₁ plus FVC was used to determine FEF_{25–75%}.

Physician diagnosis of asthma

Subjects with a completed asthma screening questionnaire and spirometry were evaluated for (1) current or previous use of asthma medication and (2) a physician diagnosis of asthma made by a hematologist or primary care physician. Asthma diagnosis was later confirmed by a pulmonologist upon referral. Physician diagnosis of asthma was based on individual physician’s clinical assessment. Physicians at the time of diagnosis or prescribing asthma medication were unaware of the asthma screening questionnaire’s data. Medical records were then reviewed midway and 6 months after the study period and categorized as “asthma” ($n=13$) if both physician diagnosis of asthma and current asthma medication prescription were present; “no asthma” ($n=26$) if no physician diagnosis of asthma and no past or current asthma medication prescription were noted; or “unclassified” ($n=2$) if past or

FIG. 1. Consort diagram of population. Hb S β^0 , sickle- β -thalassemia; Hb SS, hemoglobin SS.

current asthma medication prescription was provided but without a physician diagnosis of asthma.

Acute chest syndrome

Based on chart review, acute chest syndrome (ACS) was defined as findings of (1) a new pulmonary infiltrate on chest X-ray, (2) fever $\geq 38^{\circ}\text{C}$, and (3) presence of new respiratory symptom (chest pain, tachypnea, wheezing, cough, or hypoxia). Recurrent pneumonia was defined as three or more hospitalizations with a diagnosis of ACS and/or pneumonia as documented in the chart.

Statistical analysis

Analyses were conducted using Stata v12 statistical software (StataCorp LP, College Station, TX). The validity of each survey item as a case-detection tool for asthma was evaluated through calculation of standard parameters (i.e., sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) and application of univariate discriminate analysis procedures. 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 chi-square or Fisher's exact tests. Variance is reported using standard deviations (*SD*) or interquartile ranges (*IQR*).

Results

A total of 41/51 eligible patients (80%) completed the asthma screening questionnaire and spirometry. Of these, 21 (51.2%) had evidence of airway obstruction. Baseline demographics, previous respiratory complications, affirmative response to each component on the asthma detection survey, atopic risk factors, and hematological parameters, including hemoglobin, hematocrit, MCV, reticulocyte, WBC, neutrophil count, neutrophil percentage, lymphocyte count, lymphocytes percentage, eosinophil count, eosinophil percentage, and platelet count, were not significantly different ($p > 0.05$) between the obstructive and nonobstructive groups (See Supplementary Table S1).

Of the 39 patients with a physician diagnosis, 13 (33.3%) were categorized as asthma (Fig. 1). Eleven of the 13

TABLE 1. DEMOGRAPHICS, CLINICAL FEATURES, AND HEMATOLOGICAL RESULTS BASED ON PRESENCE OR ABSENCE OF PHYSICIAN DIAGNOSED ASTHMA IN SCD CHILDREN

	Asthma (n = 13)	No asthma (n = 26)	p-Value
<i>Demographics</i>			
Sex, % male	5 (38)	16 (62)	0.173
Age at visit, years	8.7 (0.8)	11.1 (0.8)	0.076
Hydroxyurea, n (%)	9 (69)	19 (73)	0.801
Acute chest syndrome, n (%)	8 (62)	8 (31)	0.066
Recurrent pneumonia (≥ 3 admissions), n (%)	6 (46)	4 (15)	0.038
<i>Response to asthma detection survey, n (%)</i>			
Q1 Asthma	4 (33)	0 (0)	0.007
Q1 Cough	9 (75)	7 (27)	0.005
Q1 Trouble breathing	5 (42)	3 (12)	0.083
Q1 Bronchitis	3 (25)	3 (12)	0.357
Q1 Chest tightness	6 (55)	2 (8)	0.006
Q2 ED	6 (46)	6 (23)	0.163
Q3 Missed school	8 (62)	7 (27)	0.036
Q4 Exercise	9 (69)	6 (23)	0.005
Q5 Medication	9 (69)	4 (16)	0.003
Q6 Daytime	9 (69)	5 (19)	0.004
Q7 Night	9 (69)	7 (27)	0.011
<i>Atopy, n (%)</i>			
Either parent has asthma, %	2 (15)	2 (8)	0.589
Allergic rhinitis, % with "yes"	6 (50)	3 (13)	0.036
Eczema, % with "yes"	6 (50)	7 (29)	0.281
<i>Lung function test^a</i>			
Baseline FEV ₁ , %predicted	78 (71–87)	81 (77–92)	0.283
Baseline FVC, %predicted	80 (76–86)	84 (75–93)	0.512
Baseline FEV ₁ /FVC, %predicted	95 (91–100)	101 (96–105)	0.132
Baseline FEF _{25–75} %	65 (48–81)	87 (65–105)	0.036
Obstructive airway, %	62	38	0.196
<i>Hematological^b</i>			
Hemoglobin (g/dL)	8.8 (0.4)	8.7 (0.3)	0.787
WBC ($10^3/\mu\text{L}$)	13.2 (1.3)	10.8 (0.9)	0.127
Eosinophil count ($10^3/\mu\text{L}$) ^a	0.3 (0.2–0.8)	0.3 (0.2–0.4)	0.396

Data presented as *M* (*SD*) unless otherwise indicated. Statistically significant values are shown in bold.

^aData presented as median (interquartile range).

^bOnly pertinent hematological parameters included.

SCD, sickle cell disease; FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity; FEF^{15–27}, forced expiratory flow; WBC, white blood cells; ED, Emergency Department.

TABLE 2. VALIDITY OF SURVEY ITEM AS A CASE IDENTIFICATION TOOL COMPARED WITH OBSTRUCTIVE AIRWAY

Questions	Sensitivity	Specificity	PPV	NPV
Q1 Asthma	10% (2/20)	89% (16/18)	50% (2/4)	48% (16/34)
Q1 Cough	48% (10/21)	58% (11/19)	56% (10/18)	50% (11/22)
Q1 Trouble breathing	19% (4/21)	72% (13/18)	43% (4/9)	43% (13/30)
Q1 Bronchitis	14% (3/21)	83% (15/18)	50% (3/6)	45% (15/33)
Q1 Chest tightness	32% (6/19)	83% (15/18)	67% (6/9)	54% (15/28)
Q2 ED	43% (6/20)	67% (12/18)	50% (6/6)	46% (12/26)
Q3 Missed school	40% (8/20)	63% (12/19)	53% (8/15)	50% (12/24)
Q4 Exercise	40% (8/20)	63% (12/19)	53% (8/15)	50% (12/24)
Q5 Medication	40% (8/20)	72% (13/18)	62% (8/13)	52% (13/25)
Q6 Daytime	35% (7/20)	68% (13/19)	54% (7/13)	50% (13/26)
Q7 Night	40% (8/20)	58% (11/19)	50% (8/16)	48% (11/23)
Abbreviated algorithm	40% (6/15)	75% (15/20)	55% (6/11)	50% (15/30)

PPV, positive predictive value; NPV, negative predictive value.

patients (84.6%) with a physician diagnosis of asthma were subsequently diagnosed with persistent asthma and placed on controller medication after evaluation by pulmonologists. Baseline demographic data were similar in both groups (Table 1), though previous respiratory complication rates were significantly higher in the asthma group for recurrent pneumonia (46%; $p=0.038$) and not significantly higher for acute chest syndrome (62%; $p=0.066$).

Based on the screening questionnaire, children in the asthma group had significantly higher self-reported symptoms of asthma (33%; $p=0.007$), cough (75%; $p=0.005$), trouble breathing (42%; $p=0.083$), and chest tightness (55%; $p=0.006$). There were also significantly higher reports of respiratory-related missed school days (62%; $p=0.036$), medication use (69%; $p=0.003$), exercise (69%; $p=0.005$), daytime symptoms (69%; $p=0.004$), and night symptoms (69%; $p=0.011$) in the asthma group. Instances of either a parent with a history of asthma or a diagnosis of eczema in the patient were not significantly different between the asthma and no asthma groups. Presence of allergic rhinitis was significantly higher (50%; $p=0.036$) in the asthma group. There were no differences in baseline values for FEV1, FVC, or FEV1/FVC, but FEF_{25–75%} in the asthma group was significantly lower. There were no significant hematological parameter differences between the asthma and no asthma groups.

Based on scoring of the asthma screening questionnaire using the complete algorithm (Models A–G), only three

patients (each in Model A, C, and G) fulfilled the algorithm criteria. Using obstructive pattern on spirometry as the gold standard, sensitivity (40%) and specificity (75%) of the abbreviated algorithm was poor (Table 2). Conversely, using physician diagnosis of asthma as the gold standard, the abbreviated algorithm's sensitivity (77% [95% CI 0.46–0.94]), specificity (100% [95% CI 0.84–1.00]), positive predictive value (100%), and negative predictive value (90%) were high (Table 3).

Discussion

This study carefully evaluated the question of whether a case-detection tool, previously validated in the general population, could be applied in SCD children to screen for asthma in an outpatient clinical setting.

Obstructive airway is commonly present in childhood SCD,^{9,20} probably more reflective of SCD-related airway inflammation than eosinophilic asthma inflammation,¹² thereby considerably limiting the utility of bronchial lability to screen for asthma. Lower airway obstruction is associated with pain crisis but not ACS when analyzed separately,²¹ the former not evaluated by the current study. Therefore, indistinguishable clinical characteristics of obstructive from nonobstructive airway suggest an uncertain role of spirometry in clinical management of SCD patients. Attenuation of SCD-related airway inflammation by hydroxyurea has not been thoroughly explored with a randomized control trial,

TABLE 3. VALIDITY OF SURVEY ITEM AS A CASE IDENTIFICATION TOOL COMPARED WITH PHYSICIAN DIAGNOSIS OF ASTHMA

Questions	Sensitivity	Specificity	PPV	NPV
Q1 Asthma	33% (4/12)	100% (25/25)	100% (4/4)	76% (25/33)
Q1 Cough	75% (9/12)	73% (19/26)	56% (9/16)	86% (19/22)
Q1 Trouble breathing	42% (5/12)	88% (22/25)	63% (5/8)	76% (22/29)
Q1 Bronchitis	25% (3/12)	88% (23/26)	50% (3/6)	72% (23/32)
Q1 Chest tightness	55% (6/11)	92% (22/24)	75% (6/8)	74% (20/27)
Q2 ED	46% (6/13)	77% (20/26)	50% (6/12)	79% (19/24)
Q3 Missed school	62% (8/13)	73% (19/26)	53% (8/15)	83% (20/24)
Q4 Exercise	69% (9/13)	77% (20/26)	20% (9/15)	84% (21/25)
Q5 Medication	69% (9/13)	84% (21/25)	69% (9/13)	84% (21/25)
Q6 Daytime	69% (9/13)	81% (21/26)	64% (9/14)	84% (21/25)
Q7 Night	69% (9/13)	73% (19/26)	56% (9/16)	83% (19/23)
Abbreviated algorithm	77% (10/13)	100% (26/26)	100% (10/10)	90% (26/29)

although no association with airway obstruction was observed in the present study population.

Diagnosis of asthma in SCD is complicated by an ambiguous approach based on physician diagnosis, the validity of which remains untested. Prevalence of physician diagnosed asthma in the present study population (33.3%) was in accordance with a previous report (28.3%).¹³ Nevertheless, the lack of a universal definition may result in underestimation of the true asthma prevalence of previously established physician diagnoses of asthma.^{22,23} Increased pulmonary complications with asthma are consistent with earlier findings.^{1,24} The FEV₁/FVC ratio is an important distinguishing factor between non-SCD children with asthma and otherwise healthy children.²⁵ The lack of a baseline FEV₁/FVC difference between the asthma and no asthma groups could be due to attenuation by controller medication in the asthma group or SCD-related obstructive ventilatory impairment in the no asthma group. A greater FEF_{25–75%} impairment, but normal FEV₁ and FEV₁/FVC, may be a marker of more severe hyper-responsiveness of smaller airways in subjects with asthma in SCD. The absence of distinguishing laboratory features between the asthma and no asthma groups was in agreement with a recent report.¹³

The asthma screening questionnaire was previously validated in three diverse ethnic groups, in both inner-city and suburban settings. However a similar rigorous process in African Americans was not performed.¹⁵ Therefore the seven-element response of the study population could be limited by ethno-socioeconomic factors influencing results of the complete algorithm. Interestingly, the three questions' abbreviated algorithm resulted in excellent sensitivity and specificity with a physician diagnosis of asthma, in particular for persistent asthma. Unique to this questionnaire was the incorporation of wheezing with other symptoms, including cough, trouble breathing, and chest tightness, instead of using wheezing as a stand-alone diagnostic tool, for reasons given previously.^{7,26–29} The outcome of question 1 (asthma) as a stand-alone criterion with low sensitivity but high specificity was similar to results of using wheezing as a stand-alone criterion in the general population.¹⁵ Wheezing after exercise and wheezing in association with shortness of breath, which were distinguishing features in children with SCD having asthma from those without,¹³ were evaluated by question 4 (exercise-related respiratory symptoms) and question 6 (daytime respiratory symptoms) of the abbreviated algorithm in the current study.

Atopic risk, in particular having a parent with asthma as a distinguishing feature in physician diagnosis of asthma,¹³ was not replicated in this study. Allergic rhinitis alternatively could be used as an added differentiating characteristic for future studies. Allergen sensitization was not evaluated in this study, although this approach may have limited added value in diagnosing asthma in SCD.¹³

Certain limitations need to be addressed. The asthma screening questionnaire was originally developed and validated in the general population in a school environment to overcome selection bias. In the present study, the questionnaire was nonselectively applied in an outpatient clinic setting on patients with SCD as a novel approach. Hence, this single institutional experience with limited sample size would need to be replicated in a larger study. The best standard is the asthma specialist who, in a blinded manner, thoroughly examines the study population.^{30,31} However, in

order to maintain a “real-world” scenario where asthma specialists are typically unavailable, subjects of this study were initially evaluated by a hematologist or primary care physician based on individual assessment in a blinded manner, later confirmed on referral to an asthma specialist. The case detection tool is intended to identify children who are likely to have asthma-related respiratory difficulties, including children with previously diagnosed asthma not receiving adequate controller therapy as well as undiagnosed children. While it was possible to evaluate for prescription of controller medication in 11/13 asthma patients (84.6%), comparable with 83% (44/53) of the sickle cell anemia asthma and sleep cohort,¹³ intermittent asthma may have been underdiagnosed. On the other hand, overdiagnosis did not seem to be an issue using the questionnaire, with no false positive cases detected. Finally, it is uncertain if early detection of asthma could lead to improved outcome or if increased SCD complications are related to asthma severity.

This study has important implications. It demonstrates that a validated asthma screening tool intended for the general population is relevant in SCD. As a result, it is ascertained using this tool that physician diagnosis of asthma in SCD is a valid diagnostic approach. Physician diagnosis of asthma can be assessed objectively and applied uniformly in clinical trials. The finding that the questionnaire is highly sensitive and specific in screening for asthma in an outpatient clinic setting suggests that hematologists and primary care practitioners can effectively identify at-risk individuals.

Author Disclosure Statement

No competing financial interests exist.

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