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Wheezing is common in children with sickle cell disease when compared to controls

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Abstract

In children with sickle cell disease (SCD), wheezing may occur in the absence of asthma. However, the prevalence of wheezing in children with SCD when compared to children without SCD (controls) in the same setting is unknown. Using a case-control study design, we tested the hypothesis that children with SCD would have a higher rate of wheezing than those without SCD. We enrolled 163 children with SCD (cases) and 96 children without SCD (controls) from a community hospital in Nigeria. Parent reports of respiratory symptoms were identified based on responses to questions taken from the American Thoracic Society Division of Lung Diseases' questionnaire. The median age was 8.5 years for children with SCD and 7.7 years for controls.

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Cases were more likely than controls to report wheezing both with colds (17.3% vs. 2.1%, $P<0.01$) and without colds (4.9% vs. 0%, $P=0.03$). Cases had 9.8 times greater odds of wheezing (95% CI=2.3, 42.2). In the multivariable model, the only variable associated with wheezing was SCD status (odds ratio =18.7, 95% confidence interval 2.5-142; $P=0.005$). Children with SCD experience a significantly higher rate of wheezing when compared to similar aged children without SCD.

Keywords

Sickle Cell Disease; Wheezing; Asthma; Nigeria

Introduction

Sickle cell disease (SCD) and its complications result in significant morbidity and mortality, posing a significant public health challenge worldwide¹. SCD and its societal costs disproportionately affect Africa. 85% of all children with sickle cell disease worldwide are born in Africa², and 75% of the children born in Sub-Saharan Africa have SCD³. Nigeria in particular has the largest population of children and adults with SCD in the world. Approximately 150,000 children are born with SCD each year in Nigeria⁴, compared to approximately 1,100 children born in the US each year⁴. A greater understanding of the pulmonary factors contributing to morbidity and mortality among children with SCD may lessen the public health burden of SCD worldwide.

Pulmonary complications are leading causes for morbidity and mortality in SCD^{5, 6}. Current evidence suggests that among adults, SCD in the absence of a physician diagnosis of asthma can result in wheezing, vaso-occlusive pain, acute chest syndrome and death^{7, 8}. Understanding the epidemiology of wheezing in SCD may lead to targeted therapy, such as inhaled corticosteroids, for individuals with recurrent wheezing.

Asthma and SCD-associated lung disease share many features. However, current evidence suggests that they are distinct entities. Boyd et al. found that 17% of children with SCD in the United States have a diagnosis of asthma^{9, 10}, which is similar to a background rate of 20% with probable asthma among inner-city schoolchildren in the United States¹¹. In France, the prevalence of asthma among children with SCD is 8.4%¹², which is similar to a background rate of 9.1% among children of African descent living in France¹³. In both studies, rates of respiratory symptoms in children with and without SCD were not obtained at the same time. Children with SCD demonstrate an increased prevalence of airway hyper-responsiveness and obstructive lung disease in the absence of asthma¹⁴⁻¹⁹. These findings are supported by studies demonstrating increased large and small airway resistance²⁰ as well as heightened pulmonary and systemic inflammatory responses²¹ in SCD mouse models without added allergic sensitization. A greater understanding of SCD-associated lung disease and its risk factors may allow for targeted interventions to reduce the risk of morbidity and mortality in SCD.

The primary aim of this study is to determine the prevalence of wheezing among children with and without SCD. To provide evidence that wheezing occurs more frequently in

children with SCD, we tested the hypothesis that children with SCD would have a higher rate of wheezing when compared to children without SCD. We selected a previously unstudied population of children with SCD in Nigeria. Findings supporting our hypothesis in this population would provide evidence that children with SCD have a lung phenotype associated with obstructive airway disease.

Materials and Methods

Ethical research approval was obtained at Murtala Mohammed Specialist Hospital (MMSH) in Kano, Nigeria. Institutional Review Board (IRB) approval was obtained at Vanderbilt University School of Medicine (VUSM) in Nashville, Tennessee, USA. We employed a case-control study design. Subjects were recruited at MMSH over a 4-month period. A research assistant interviewed 250 consecutive cases (children with SCD) presenting to the SCD specialty clinic for routine care, and 250 consecutive controls (children without SCD) presenting to the general pediatric clinic for routine complaints such as fever, acute respiratory illness, and diarrhea. In order to exclude possible cases of transient wheezing in young children, we limited our final analysis to children ages four and older, resulting in 163 cases and 96 controls.

A structured questionnaire captured participants' demographic information, medical history (e.g., respiratory symptoms, allergies), environmental factors (e.g., cooking, presence of animals in the home), and parental behavior (e.g., smoking). Respiratory symptoms reported by parents were based on responses to questions taken from the American Thoracic Society Division of Lung Diseases' Questionnaire (ATS-DLD-78-C)²². The questionnaire was translated into the native language (Hausa) by a professional translator. A senior member of the team in Nigeria randomly interviewed 50 families and confirmed the responses to the questionnaires. Responses were recorded on paper, translated into English, and entered into a REDCapTM electronic research database by a research assistant in Nigeria. Subsequently the paper questionnaires were photocopied and mailed to VUSM. Research staff in the United States then re-entered the data into the REDCapTM electronic research database and compared the results to those that were entered in Nigeria. Greater than 95% concordance was reached between the data entry in Kano, Nigeria, and Nashville, TN, USA. Data analysis was performed by research staff at Vanderbilt University Medical School using IBM SPSS 20 for Windows 32-bit. Chi-square test of association and Fisher Exact Test were used for categorical variables. Wilcoxon rank-sum test and Kruskal-Wallis U test were used for continuous and ordinal variables. Multivariate logistic regression was used to determine the association of variables to wheezing. Of the 259 subjects age 4 and above, 244 are included in the multivariate analysis (15 were excluded due to missing data in any covariate). Independent covariates include age, gender, sickle cell disease status (present or absent), household income, head of household education status, and source of fuel (firewood/charcoal or kerosene). The dependent covariate was any wheezing, defined as a positive response to any of the three wheezing questions: wheezing with colds, wheezing without colds, and wheezing with exercise.

Results

Demographics

The median ages for children with SCD and controls were 8.5 years and 7.7 years, respectively ($P=0.1$, Table 1). No differences in gender, ethnicity, educational achievement of head of household, household income, place of residence, or school attendance were observed between children with and without SCD.

History of wheezing and eczema

Children with SCD reported higher rates of wheezing with colds (17.3% vs. 2.1%, $P<0.01$) and without cold (4.9% vs. 0.0%, $P=0.03$) (Table 2). One participant in both groups reported a history of wheezing attack with shortness of breath (0.6% vs. 1.0%, $P=0.7$). Combining results from the 3 wheezing-related questions, children with SCD were more than 9 times as likely to wheeze than controls (odds ratio [OR]=9.8, 95% confidence interval [CI]=2.3, 42.2). The prevalence of a physician diagnosis of eczema was low in both groups. Children with SCD reported higher rates of eczema, but this difference was not statistically significant (4.9% vs. 1.0%, $P=0.2$). Birth history, maternal history of asthma, tobacco exposure, cooking fuel, and presence of animals in the home did not differ significantly between cases and controls (Table 3). Outdoor exposures were not assessed as they are not included in the standardized questionnaire used for this study.

Association of risk factors to wheezing

With any wheezing as the dependent covariate, we used a multivariable logistic regression model of association between asthma risk factors and SCD status, which was statistically significant ($P=0.002$). In this model, the only variable significantly associated with wheezing was SCD status ($P=0.005$, odds ratio [OR]=18.7, 95% confidence interval [CI]=2.5, 142). Age was not a significant variable ($P=0.68$, odds ratio [OR]=0.97, confidence interval [CI]=0.84, 1.1). When SCD was excluded as a risk factor, the model was no longer significantly predictive ($P=0.7$).

Discussion

Asthma and wheezing are a result of both genetic and environmental factors. Determining whether there is an increase in the prevalence of asthma symptoms in a population distinct from North America and Europe, with different genetic and environmental factors, may help elucidate common factors. To our knowledge this is the first study in sub-Saharan Africa demonstrating that clinical signs of obstructive lung disease (i.e. wheezing) occur with a higher frequency in children with SCD when compared with controls that have the same genetic background and environmental exposures.

The association between pulmonary disease and increased morbidity and mortality in SCD is well established^{5, 6}. However, what is not clear is whether wheezing is more common in children with SCD when compared to children without SCD. Determining whether children with SCD have an increased rate of wheezing is particularly important, because wheezing is

the most common respiratory finding occurring in SCD²³ and is associated with a physician diagnosis of asthma that requires daily medication²³.

We postulated that children with SCD would have a higher prevalence of wheezing than children without SCD, a lung phenotype associated with obstructive airway disease. Our findings demonstrate a high prevalence of wheezing among children with SCD when compared to contemporary controls recruited from the same clinic population distinct from other previously studies populations in US⁶ and Europe¹². Within our study population, children with SCD were greater than 9 times more likely to wheeze than controls. Using multivariable logistic regression, the only statistically significant factor associated with wheezing was SCD status. No asthma risk factors, including environmental tobacco smoke exposure²⁴, maternal history of asthma²⁵ and poverty²⁶, were found to be associated with parental report of wheezing. Taken together, these data strongly support, but do not confirm, the premise that SCD alone may result in wheezing^{7,8}.

Our case-control study design has inherent limitations, the major one being recall bias. Our data are based on responses obtained from parents, not from the medical record. The estimated prevalence of wheezing may have been higher in children with SCD, as parents of children with SCD and respiratory symptoms may have sought medical attention more often and may be more able to describe wheezing. Although plausible, we do not believe that this is a likely explanation, given that the majority of questions answered by the parents did not demonstrate a statistically significant difference between the two groups. The ability to compare cases and controls that come from the same population, with data collected during the same time, allows for more meaningful comparisons between the cases and controls. We elected not to include a diagnosis of asthma in this study because asthma requires a physician diagnosis which can be variable²⁷.

A perceived weakness of the study is the parental report of asthma symptoms, as opposed to a physician report of asthma symptoms. However, parental report of asthma symptoms has been validated against physician diagnosis of asthma²⁸. Also, parental report of asthma-like symptoms in the previous 12 months has been demonstrated to correlate with a prospective daily diary²⁹. Thus, we believe our strategy of using parental reporting of wheezing is a valid assessment in both the cases and controls.

Prior to starting the study, we were not aware of the age distribution of the general pediatric clinic and the sickle cell disease clinic. Based on evaluating consecutive patients, the age distribution of the two clinics were quite different, with the general clinic population being significant younger. In our analysis, we elected to exclude participants less than 4 years of age, because this is the age group most likely to have transient wheezing due to the small caliber of the airways which resolves with airway growth^{30, 31}. The exclusion of younger participants allowed us to have better matched cases and controls, and to focus on persistent, not transient, pulmonary manifestations which have a long term impact on morbidity or mortality in SCD.

We were not able to detect a difference in physician diagnosis of atopic diseases such as asthma as eczema, primarily because prevalence is low among children with and without

SCD. The low rate of asthma diagnosis is particularly surprising given the high rate of wheezing among subjects. The reason for this is unknown and should be investigated further.

In summary, children with SCD experience a dramatically higher rate of wheezing compared to children without SCD, and asthma risk factors alone do not appear to account for the higher rate of wheezing. We posit that there may be a separate pathogenic process for wheezing in children with SCD when compared children without SCD.

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Table 1

Participant demographics, children age 4 and older with and without sickle cell disease (SCD), Kano, Nigeria.

	SCD (n=163)	Controls (n=96)	P
Female, n (%)	77 (47.2%)	54 (56.2%)	0.2
Age [†]	8.5 (5.7, 11.6)	7.7 (5.7, 9.8)	0.1
Ethnic group, n (%)			1.0 [‡]
Bajju	1 (0.6%)	0 (0.0%)	
Bendelite (Esako)	0 (0.0%)	0 (0.0%)	
Hausa-Fulani	162 (99.4%)	95 (99.0%)	
Yoruba	0 (0.0%)	1 (1.0%)	
Highest education, head of household, n (%) [§]			0.3
None	50 (32.3%)	30 (33.3%)	
Primary School	19 (12.3%)	10 (11.1%)	
Secondary School	57 (36.8%)	25 (27.8%)	
Higher Education	29 (18.7%)	25 (27.8%)	
Household income per year in US dollars, n (%)			0.4 [¶]
<\$318	54 (33.1%)	29 (30.2%)	
\$318 – \$634	30 (18.4%)	31 (31.3%)	
\$635 – \$1269	25 (15.3%)	9 (9.4%)	
\$1270 – \$1904	28 (17.2%)	12 (12.5%)	
\$1905 – \$2540	15 (9.2%)	8 (8.3%)	
>\$2540	11 (6.7%)	7 (7.3%)	
Primary place of residence (past 3 yrs), n (%)			0.6
Ibadan	1 (0.6%)	0 (0.0%)	
Kano	161 (98.8%)	96 (100.0%)	
Lagos	1 (0.6%)	0 (0.0%)	
Attends any school	157 (96.3%)	88 (91.7%)	0.2

[†]Median (interquartile range)[‡]Hausa-Fulani vs. other, using Fisher's exact test.[§]Excludes Refused/Missing[¶]Less than \$1270 vs. greater than \$1270, using Mantel-Haenszel Chi-square

Table 2

History of wheezing, and eczema in children age 4 and older with and without sickle cell disease (SCD), Kano, Nigeria.

	SCD (n=163)	Controls (n=96)	P
Wheezing			
Chest ever sounds wheezy or whistling with colds, n (%)	28 (17.3%)	2 (2.1%)	<0.01
Chest ever sounds wheezy or whistling without having a cold, n (%)	8 (4.9%)	0 (0.0%)	0.03
Ever had an attack of wheezing that caused shortness of breath, n (%)	1 (0.6%)	1 (1.0%)	0.7
Ever diagnosed with eczema, n (%)	8 (4.9%)	1 (1.0%)	0.2

Table 3

Birth history, family history, and environmental exposures, in children age 4 and older with and without sickle cell disease (SCD), Kano, Nigeria.

	SCD (n=163)	Controls (n=96)	P
Birth history			
Delivered via Caesarean section, n (%)	2 (1.2%)	0 (0.0%)	0.5
Gestational age (weeks) [†]	39 (38, 39)	39 (39, 39)	0.2
Parental history of asthma			
Mother, n (%)	2 (1.2%)	0 (0.0%)	0.5
Tobacco exposure			
Exposed to smoking from birth to 2 years old, n (%)	6 (3.7%)	5 (5.2%)	0.6
Cooking fuel			
Firewood/charcoal, n (%)	129 (79.1%)	71 (74.0%)	0.3
Gas, n (%)	7 (4.3%)	2 (2.1%)	0.5
Kerosene, n (%)	61 (37.4%)	40 (41.7%)	0.5
Animal in home, n (%)	62 (38.0%)	30 (31.2%)	0.4

[†] Median (interquartile range)