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Abnormal pulmonary function and associated risk factors in children and adolescents with sickle cell anemia

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Abstract

Obstructive and restrictive pulmonary changes develop in children with sickle cell disease, but reports conflict as to the type of change that predominates. We prospectively performed spirometry, plethysmography and lung diffusing capacity in 146 children aged 7–20 years with hemoglobin SS or S β^0 -thalassemia. Nineteen percent of the patients had obstructive physiology as defined according to guidelines of the American Thoracic Society. In addition, 9% had restrictive physiology and 11% had abnormal but not categorized physiology. Increasing age, patient- or family-reported history of asthma or wheezing, and higher lactate dehydrogenase concentration were independent predictors of obstruction as reflected in lower FEV1/FVC. In conclusion, abnormal pulmonary function, most often obstructive, is common in children with hemoglobin SS and S β^0 -thalassemia. Full pulmonary function testing should be performed in children with hemoglobin SS or S β^0 thalassemia, especially with history of asthma or wheezing and accentuated elevations in hemolytic markers.

Keywords

sickle cell anemia; pulmonary function tests; obstructive pulmonary function; lactate dehydrogenase; reticulocyte count

Introduction

Restrictive pulmonary function has been observed in 35% or more of adults with sickle cell disease and obstructive function in less than 20% [1–3]. Obstructive function has been reported in 5% to 35% of children and adolescents with sickle cell disease [4–8] and restrictive function in 8% to 22% [4–8]. Airway hyper-responsiveness is also common [9–11] but may not be associated with a history of asthma [12]. One study reported progressive obstructive pulmonary abnormalities in children with sickle cell disease followed over time [13]. Lower airway obstruction has been associated with an increased rate of hospitalization for pain or acute chest syndrome in children with sickle cell disease [5].

The Pulmonary Hypertension and Hypoxic Response in SCD (PUSH) study is a prospective, observational multicenter program initiated in 2006 to investigate the prevalence, risk factors and clinical consequences of elevated estimated pulmonary artery systolic pressure in children and adolescents with sickle cell disease [14]. This report focuses on the subgroup of children in the PUSH study who performed pulmonary function testing. We describe the patterns of pulmonary function abnormalities and determine their risk factors.

Materials and Methods

Research participants

The Institutional Review Boards of Howard University (No. 05-SCD-01), Children's National Medical Center (No. 3822), University of Michigan (No. HUM00005457) and the intramural National Heart, Lung and Blood Institute (No. 07-H-0181) approved the research. Written informed consent was obtained for each participant. Individuals 3 to 20 years of age with sickle cell disease were enrolled into the PUSH study and evaluated at steady state (N = 505). The study was prospectively designed to offer pulmonary function testing to children 7 years of age (n = 399) if a pulmonary function laboratory was available at the time of the study, and those who underwent pulmonary function testing are the subject of this paper (N = 184). Those who underwent pulmonary function testing did not differ from those who did not in terms of age, gender, genotype, history of asthma or wheezing, hemoglobin concentration or tricuspid regurgitation velocity. This report focuses on patients with hemoglobin SS or S β^0 thalassemia. Participants were tested under steady state conditions defined as absence of hospitalization or emergency department visit for pain crisis, infection or other complication for at least three weeks. A history of acute chest syndrome, was obtained. Included in the category of acute chest syndrome are many episodes of acute chest syndrome or pneumonia that were confirmed by review of medical records, but also events that were patient- or family-reported but for which medical record review was not accomplished. A history of asthma or wheezing was based on answering yes to the question as to whether there was a "medical history of asthma or wheezing". However, a systematic chart review was not performed for each patient.

Pulmonary function testing

Participants performed spirometry, plethysmography (measurement of lung volumes), and lung diffusion capacity for carbon monoxide (DLCO) according to American Thoracic

Society/European Respiratory Society (ATS/ESR) standard protocols.[15–17] The testing systems used were VMAX 62J (Sensomedics, Vienna, Austria) at the University of Michigan and Howard University and Elite DX (Medical Graphics, St. Paul, MN) at Children’s National Medical Center. Results were printed in a standardized manner and reviewed by the same investigator (M.A.) to ensure acceptability and reproducibility according to ATS/ERS standards before including them in the analysis. The following parameters were included: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), the ratio FEV1/FVC, forced expiratory flow at 25–75% of FVC (FEF25–75), total lung capacity (TLC), ratio of residual volume over total lung capacity (RV/TLC) and DLCO. Spirometry results (FVC, FEV1, FEV1/FVC and FEF25–75) were expressed as percent of the predicted value based on gender, age and ethnic appropriate reference standards [18,19]. For the FEV1/FVC ratio the actual measurement was reported. TLC was expressed as percent of predicted of race adjusted reference standards by applying a correction factor of 0.88 to the TLC predicted value for Caucasians[20]. The actual RV/TLC ratio measurement was reported. DLCO was adjusted for hemoglobin concentration and expressed as percent of predicted.

Patterns of lung function

The patients were assigned patterns of lung function on the basis of spirometry and plethysmography according to guidelines of the American Thoracic Society/European Respiratory Society[20]. Normal lung function was assigned to participants with FVC, FEV1, FEV1/FVC and FEF25–75 at or above the lower limit of normal[18] and TLC and DLCO ≥80% of predicted. Obstructive lung function was assigned to participants with FEV1/FVC and FEV1 and/or FEF 25–75 below the lower limit of normal. This definition follows the recommendations of the ATS/ERS task force [20], emphasizes the role of the FEV1/FVC as the hallmark of obstruction and puts the threshold of normality at the 5th percentile of the predicted reference value. The same document recommends the Wang et al [19] and Hankinson et al [18] publications as the reference values to be used in US populations for children and the general population respectively. The lower limits of normal in these normative papers are the percent predicted corresponding to the 5th percentile. Restrictive lung function was assigned to participants with FVC and FEV1 below the lower limit of normal with normal FEV1/FVC ratio and TLC <80% of predicted. Mixed lung function was assigned to participants with FEV1/FVC below the lower limit of normal and TLC <80% of predicted. Results that did not fit the criteria outlined above were classified as “abnormal but not classifiable”.

Clinical evaluation and laboratory testing

Participants underwent medical history, physical examination and venipuncture for complete blood count, reticulocyte count and serum chemistries. Laboratory tests were performed locally. Serum concentration of lactate dehydrogenase was considered to be a marker of hemolysis.[21] The clinical evaluation and laboratory testing were done within three weeks of the pulmonary function evaluation.

Statistical Analysis

Multivariate linear regression analysis was used to assess the significant predictors of FEV1/FVC, TLC and DLCO. Logistic regression analysis was used to assess the significant predictors of abnormal pulmonary function. We used a stepwise backward approach to build the final models; in each model potential interactions were assessed. Final models were checked for assumption, distribution of residuals and co-linearity. The analyses were performed with STATA 12.0 (College Station, TX).

Results

Clinical characteristics and pulmonary function

Spirometric results that were reproducible and acceptable according to ATS/ERS standards were obtained for 146 participants. Reproducible and acceptable plethysmographic results were obtained for 97 participants and DLCO results for 95. Hydroxyurea therapy was associated with lower lactate dehydrogenase concentration ($P = 0.046$) and white blood cell count ($P = 0.0001$) and higher FEV1/FVC ($P = 0.031$) and FEV1/FVC percent predicted ($P = 0.040$). Median values for each parameter of pulmonary function were within normal limits. One-third of the patients had FEV1 and FEF 25-75 values below the age-, gender- and ethnicity-specific reference range. Nine percent of had TLC below the reference range.

Independent predictors of FEV1/FVC, TLC and DLCO by multiple linear regression analysis (Table II)

Variables included in the analyses were age, gender, history of asthma or wheezing, history of acute chest syndrome, hemoglobin concentration, serum lactate dehydrogenase concentration and weight-for-age z-score. For the analysis of DLCO, hemoglobin oxygen saturation and TLC were also included. Older age, history of asthma or wheezing, and higher lactate dehydrogenase concentration had significant independent associations with lower FEV1/FVC by multiple linear regression. Female gender and lower weight-for-age z score had significant independent associations with lower TLC. Lower TLC was associated with a lower DLCO, while lower oxygen saturation was associated with a higher DLCO.

Patterns of pulmonary function in patients with sickle cell disease

We categorized pulmonary function only in participants who performed both spirometry and plethysmography due to the inability of the former to identify restrictive lung function accurately. For example, six of 14 patients in our cohort with an apparently restrictive finding on spirometry (low FVC and FEV1 and normal FEV1/FVC) had a normal TLC. Abnormal patterns were found in 38 (39%) of 97 patients. Nineteen percent had obstructive lung function, 9% had restrictive function, and 11% did not have normal pulmonary function but could not be classified as obstructive or restrictive. Of the 18 patients with obstructive pulmonary function, 8 (44%) had a history of asthma or wheezing. Adjusted DLCO 80% of predicted was found in 19% of 95 patients. Adjusted DLCO was significantly lower among patients with restrictive pulmonary function compared to patients with normal function ($P = 0.005$).

Discussion

In this study, 39% of children and adolescents with hemoglobin SS or S β^0 thalassemia had abnormal pulmonary function. After pulmonary function was categorized the predominant pulmonary function abnormality was obstructive. Older age, history of asthma or wheezing, and higher lactate dehydrogenase concentration were associated with obstructive pulmonary function as reflected in a lower FEV1/FVC. Our findings are in agreement with other reports in children sickle cell disease that pulmonary function worsens with increasing age [22] and that obstruction is the most common pulmonary function abnormality [4,13,23]. They are in contrast to recent reports that restrictive pulmonary function is the predominant abnormality in children with sickle cell disease [7,22].

There are a number of causes of obstructive lung disease in children, including bronchopulmonary dysplasia, cystic fibrosis, bronchiolitis, and asthma [24]. Airway hyper-responsiveness is common in most conditions associated with obstructive lung disease, including children with sickle cell disease, but may not be related to a diagnosis of asthma [12]. Other investigators have reported a high risk of complications in sickle cell disease patients with asthma [25–28]. Of special concern is the finding in the Cooperative Study of Sickle Cell Disease that asthma was associated with a more than two-fold increase in the hazards ratio of death [27]. In the present study, history of asthma or wheezing was an independent predictor of lower FEV1/FVC, but, similar to another report [28], one-half of those with obstructive physiology did not have a history of asthma or wheezing. A limitation of our study is that the self-reported history of asthma or wheezing was not confirmed by systematic chart review or evidence of an allergic diathesis. Furthermore, other investigators have suggested a difference between a clinical diagnosis of asthma and a history of wheezing without a diagnosis of asthma in sickle cell disease [29,30]. We are unable to distinguish between these two categories in our data set. Therefore another limitation of our study is that asthma and a history of recurrent wheezing related to sickle cell disease may be two different entities, but we have classified them as one entity. Nevertheless, asthma and wheezing do not appear to explain all obstructive lung function in children with sickle cell anemia in the present study.

Our findings also suggest that a greater degree of hemolysis as reflected in the lactate dehydrogenase concentration may be associated with airway obstruction; this concept is in agreement with the reported finding of an association between airway hyper reactivity and increased serum levels of lactate dehydrogenase [12]. However, the association between hemolysis and obstruction in our study is weak. Other observations suggest that sickle cell disease itself may be associated with obstructive airway disease. A recent study suggests that increased pulmonary capillary blood volume may contribute to increased airways obstruction in children with sickle cell disease [31]. In a preclinical study, Pritchard and colleagues measured positive end-expiratory pressures and performed methacholine studies in transgenic mice [32]. The sickle cell disease mice had greater resistance in large and small airways compared with hemoglobin A mice. At baseline LDH was not higher in sickle cell disease mice that were sensitized and had experimental asthma compared to control sickle cell disease mice, but IgE levels were increased in the experimental asthma sickle cell disease mice.

The association of increasing age with lower FEV1/FVC in this cross sectional analysis is consistent with a previously published longitudinal prospective study [13] reporting a progressive development of obstructive function in children with sickle cell disease. Other investigators have reported that restrictive abnormalities become more prominent with increasing age in children and adolescents with sickle cell disease [6] and that the prevalence of restrictive lung function is as high as 74% among adults [1]. It has also been proposed that obstructive lung changes occur first followed by the development of restrictive changes [4].

Limitations to our study include that medical record confirmation of asthma or wheezing was not systematically performed, that bronchodilator testing was not a routine part of the investigation, and that information on medications for reactive airway disease was not captured.

In summary, abnormal pulmonary function was predominantly obstructive and related to both a history of asthma or wheezing and a marker of hemolysis (lactate dehydrogenase). Our findings add to a body of literature suggesting that pulmonary function testing should be routinely performed in children with hemoglobin SS or S β^0 thalassemia. In patients with obstructive pulmonary function, efforts should be considered to control the degree of hemolysis with prescription of hydroxyurea or other disease modifying treatments. Other investigators have reported a high risk of complications in sickle cell disease patients with asthma [25–28]. Of special concern is the finding in the Cooperative Study of Sickle Cell Disease that asthma was associated with a more than two-fold increase in the hazards ratio of death [27]. Therefore, efforts should also be directed to identify and treat asthma in patients with obstructive pulmonary function. Further prospective and longitudinal studies should examine the mechanisms of obstructive and restrictive changes, the complications associated with these abnormalities and the relationship of these changes with increasing in age.

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Figure 1.
Patterns of pulmonary function.

Table I

Clinical characteristics and pulmonary function in children and adolescents with Hb SS or S β^0 thalassemia. Results in median (interquartile range) or no. (%).

	N	Result
Clinical information		
Age (years)	146	15 (11–17)
Female	146	65 (45%)
Height (cm)	146	159 (146–168)
Weight-for-age Z-score	145	−0.11 (−0.83–0.55)
Current use of hydroxyurea	145	51 (35%)
History of asthma or wheezing	145	42 (29%)
History of acute chest syndrome	145	79 (54%)
2+ pain episodes past year	146	34 (23%)
Hemoglobin (g/dL)	144	8.8 (7.9–9.7)
Reticulocytes (%)	139	8.9 (5.9–12.1)
Reticulocyte count ($\times 10^9/L$)	139	252 (185–338)
White blood cells ($\times 10^6/L$)	144	11.3 (8.4–13.5)
LDH** (U/L)	137	432 (341–573)
Oxygen sat. (%)	144	98 (96–99)
Pulmonary function tests: median (interquartile range) values		
FVC (% predicted)	146	90 (80–98)
FEV1 (% predicted)	146	84 (74–96)
FEV1/FVC	146	84 (81–88)
FEV1/FVC (% predicted)	146	95 (91–100)
FEF 25-75 (% predicted)	136	72 (61–91)
TLC (% predicted)	97	97 (88–109)
RV/TLC	97	25 (20–34)
DLCO (adj. for Hb)	95	96 (85–109)
Pulmonary function tests: no. (%) below the age-, gender- and ethnicity-specific reference range		
FVC	146	30 (21%)
FEV1	146	48 (33%)
FEV1/FVC	146	18 (12%)
FEF 25-75	136	46 (34%)
TLC	97	9 (9%)
DLCO (adj. for Hb)	95	17 (18%)

** LDH refers to lactate dehydrogenase

Table II

Independent predictors of specific parameters of pulmonary function by multiple linear regression* in children and adolescents with sickle cell anemia.

	Beta	95% CI	P
a. FEV1/FVC (n = 137)			
Age increase of 10 years	-4.61	-7.04 – -2.22	<0.0001
History of asthma or wheezing	-3.84	-5.86 – -1.82	<0.0001
Lactate dehydrogenase (natural log)	-2.78	-5.23 – -0.32	0.027
b. TLC percent predicted (n = 96)			
Female gender	-14	-20 – -8	<0.0001
Weight-for-age z score	5	3 – 8	0.007
c. DLCO percent predicted, adjusted for hemoglobin (n = 82)			
TLC, 10 point decrease	-7	-5 – -9	<0.0001
Hemoglobin oxygen saturation, 5 point decrease	13	19 – 7	<0.0001

* Variables entered into models were: age, sex, history of asthma or wheezing, history of acute chest syndrome, hemoglobin concentration, lactate dehydrogenase, reticulocyte count, white blood cell count and weight-for-age z score. In the DLCO model hemoglobin oxygen saturation and TLC were added to this list.

a. R-square = 0.19

b. R-square = 0.27 one outlier was removed.

c. R-square = 0.36