Association of wheeze with lung function decline in children with sickle cell disease

To the Editor:

Emerging evidence suggests that wheezing in children with sickle cell disease (SCD) is associated with higher rates of acute chest syndrome (ACS) and vaso-occlusive crises, independent of a diagnosis of asthma [1, 2]. We investigated the relationships of longitudinal pulmonary function decline with wheeze, asthma and atopy in a cohort of paediatric patients with SCD, using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [3], skin prick testing (SPT) and airway nitric oxide (NO) measurements.

Approval was obtained from the Hospital for Sick Children Institutional Research Ethics Board, and written informed consent was obtained.

Children with SCD ⩾6 years of age and able to perform pulmonary function testing (PFT) were recruited from 2006 to 2011. Subjects were excluded if they had experienced an upper or lower respiratory tract infection during the 2 weeks before PFT. Patient records were reviewed to identify those with a history of ACS, defined as a hospitalisation with chest pain, dyspnoea, and new infiltrates on chest radiograph.

Fractional exhaled nitric oxide at 50 mL·s^{-1} ($FeNO_{50}$), nasal nitric oxide (NO) (aspiration flow 330 mL·min^{-1}), and spirometry were measured and interpreted as per published guidelines [4–7]. SPT was performed on the forearm using a Multi-Test II applicator, with 14 standardised allergenic extracts (ALK-Abelló Inc., Round Rock, TX, USA). Subjects were defined as atopic if they had a wheal of 3 mm or greater in diameter, compared with saline control, to any extract.

Descriptive statistics were used for demographics, disease characteristics and PFT measures. Chi-squared test was used to assess for association between categorical variables of interest. Two-way analysis of variance (ANOVA) was used to assess the association of PFT measures with the categorical covariates of interest, adjusted for sex. Linear mixed effects model with appropriate covariance structure was used to determine the rate of PFT decline with age, and to assess for associations with potential risk factors (atopy, SCD genotype, ACS, wheezing, asthma diagnosis). All p-values were two-sided, and $p<0.05$ was used to indicate significant differences. Statistical analysis was performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

In total, 154 patients with SCD were included (table 1). No significant differences in PFT were seen between those reporting taking (n=12, 8%) or not taking asthma medications. Individuals using asthma medications, or those with the haemoglobin (Hb) HbSS genotype or prior ACS, were not more likely to have significant bronchodilator responsiveness in forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), or forced expiratory flow at 25–75% of FVC ($FEF_{25–75}$). Patients with a physician diagnosis of asthma (n=24, 22%) had lower mean $FEF_{25–75}$ compared with the rest of the cohort (71.5% *versus* 84.0% predicted, p=0.0447), but otherwise similar PFT. They were not more likely to have bronchodilator responsiveness in FEV_1, FVC, or $FEF_{25–75}$. There was a positive association between Hb and FEV_1 %predicted (r=0.29314, p=0.0002), and FVC %predicted (r=0.27105, p=0.0007). Univariable analysis revealed a significant impact of Hb on bronchodilator responsiveness in FEV_1 and FVC (OR=1.031, 95% CI 1.006–1.057, p=0.0165).

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TABLE 1 Demographics and test results of study population

Subjects n	154
Demographics	
Age years	12.6±3.3 (6–18)
Male sex n (%)	76 (49%)
Hb genotype n (%)	
HbSS	106 (69%)
HbSC	34 (22%)
HbSB$^+$thal	9 (6%)
HbSB^{0}thal	4 (3%)
HbSE	1 (1%)
History of ACS n (%)	56 (36%)
Pulmonary function testing	
FVC % predicted	86.7±14.0 (53–127)
FEV_1 % predicted	84.8±15.0 (48–118)
FEV_1/FVC %	86.1±6.1 (64–98)
$FEF_{25–75}$ % predicted	84.4±29.9 (31–261)
12% change in FEV_1 or FVC n (%)	20 (13%)
30% change in $FEF_{25–75}$ n (%)	46 (30%)
ISAAC questionnaires[#]	
Physician diagnosis of asthma n (%)	24 (22%)
History of ever having wheezed n (%)	42 (39%)
History of recent wheezing n (%)	21 (19%)
Airway nitric oxide measurements[¶]	
Fractional exhaled nitric oxide ppb	17.9±15.9 (2–102)
Nasal nitric oxide ppb	890±387 (16–3146)
Rate of decline in FEV_1/FVC[+]	
History of recent wheezing % (95% CI)	0.90 (0.61–1.19)
No history of recent wheezing % (95% CI)	0.33 (0.22–0.44)

Data are presented as population mean±SD, unless otherwise stated. Values in parentheses represent minimum/maximum ranges, unless otherwise stated. Spirometric values were derived from the Hankinson equations [6]. Hb: haemoglobin; ACS: acute chest syndrome; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75}$: forced expiratory flow at 25–75% of FVC; ISAAC: International Study of Asthma and Allergies in Childhood. [#]: n=108; [¶]: n=144; [+]: n=97.

Of the 154 SCD subjects, 80 (52%) were atopic by SPT. There were no differences in PFT results, rates of bronchodilator responsiveness or ACS frequency between atopic and non-atopic patients. ISAAC questionnaires were completed by 108 subjects (70%). Among this group, 54 (50%) were atopic according to SPT. Rates of physician diagnosis of asthma and recent/remote wheezing were not different between the atopic and non-atopic groups.

There was no relationship between $FeNO_{50}$ or nasal NO and ACS history, bronchodilator responsiveness, asthma diagnosis or history of wheezing. There was no relationship between nasal NO and atopic status. However, atopic individuals had higher mean $FeNO_{50}$ compared with non-atopic individuals (21.22 ppb *versus* 14.65 ppb, p=0.035).

Longitudinal PFT data were available for 137 subjects (after excluding those taking asthma medications), with an average of six (2–14) measurements per person. The SCD genotype HbSS was the strongest risk factor for decline in PFT after adjusting for age and sex. Neither atopy nor provided ACS history added effect on PFT decline. Of those who completed ISAAC questionnaires, 97 had longitudinal PFT data available for analysis. After adjusting for age, sex, prior ACS and SCD genotype, a history of ever having wheezed was associated with a 3.1% lower FEV_1/FVC ratio (p=0.0001) and 12.4% predicted lower $FEF_{25–75}$ (p=0.005) at all time points. There was no effect of asthma diagnosis, atopy or history of wheezing (recent or remote) on the rate of decline in FVC, FEV_1 or $FEF_{25–75}$, but a history of recent wheezing (within the past year) was a significant predictor of rate of decline in FEV_1/FVC (see table 1).

To our knowledge, this is the first longitudinal study to show that in children with SCD, the clinical phenotype of wheezing is associated with more rapid PFT decline over time. This association, while seen exclusively in measures of airway obstruction, was independent of a diagnosis of asthma. A hallmark of asthma in the general population, and a key diagnostic feature, is reversible airflow limitation [8]. In this SCD cohort, 13% had significant bronchodilator responsiveness in either FEV_1 or FVC, according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria, and 30% had an

improvement of ⩾30% in $FEF_{25–75}$ following bronchodilator administration. However, using either published ATS criteria for bronchodilator response [7] or improvement of ⩾30% in $FEF_{25–75}$, the rates of bronchodilator responsiveness in our cohort were considerably lower than asthma rates reported in other SCD studies, in which up to 53% of participants were diagnosed with asthma [9]. When the ISAAC questionnaires from our study were reviewed, a possible explanation for these discrepancies emerged. While 22% of patients reported a physician diagnosis of asthma, 38% had a history of wheezing, with 19% reporting wheezing within the past year. Thus, inconsistent use of diagnostic criteria, including physician diagnosis, patient symptom report or reversible airflow limitation on PFT, may contribute to the wide variation in asthma prevalence reported in SCD populations in the existing literature [9–12].

In this cohort of paediatric patients with SCD from Toronto, half were atopic, with patient-reported wheezing and physician-diagnosed asthma rates comparable between atopic and non-atopic participants. Similar results were obtained by KNIGHT-MADDEN *et al.* [10], who identified a significant proportion of non-atopic asthmatic patients in their Jamaican paediatric SCD population. Mean $FeNO_{50}$, a marker of eosinophilic airways inflammation and asthma, was slightly elevated in our atopic compared with our non-atopic patients, but neither was increased from normal reference values [13]. Thus, summarising our observations, the previously established links between asthma and morbidity in the SCD population may be better expressed as an association between wheezing and morbidity. A limitation of our study is a lack of assessment of additional markers of disease severity, which could help to elucidate the links between respiratory symptoms and overall SCD status.

GLASSBERG *et al.* [14] hypothesised that wheezing in SCD may represent an intrinsic component of SCD-related lung disease, rather than asthma, congruent with our findings, with increased capillary blood volume at least partly explaining airway obstruction in this population [15]. SCD-modifying therapies such as hydroxyurea may therefore be more appropriate than asthma therapy for treatment of the underlying causes for wheeze in these patients. This is supported by the recent observation that hydroxyurea therapy resulted in improved PFT decline in treated children with sickle cell anaemia [16]. Further study is required to establish the pathophysiology underlying wheeze and airflow limitation in children with SCD, as well as investigation into appropriate therapies that will improve lung health in these patients.

Glenda N. Bendiak[1], Dimas Mateos-Corral[2], Anwar Sallam[3], Eshetu G. Atenafu[4], Melanie Kirby[5], Isaac Odame[5], Peter Bikangaga[3], Padmaja Subbarao[3,6] and Hartmut Grasemann[3,6]
[1]Section of Respiratory Medicine, Dept of Pediatrics, Alberta Children's Hospital, Calgary, AB, Canada. [2]Division of Pediatric Respiratory Medicine, Dept of Pediatrics, IWK Health Centre, Halifax, NS, Canada. [3]Division of Respiratory Medicine, Dept of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada. [4]Biostatistics Dept, University Health Network, Toronto, ON, Canada. [5]Division of Hematology and Oncology, Dept of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada. [6]Program in Physiology and Experimental Medicine, SickKids Research Institute, The Hospital for Sick Children, and University of Toronto, Toronto, ON, Canada.

Correspondence: Hartmut Grasemann, Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada M5G 1X8. E-mail: hartmut.grasemann@sickkids.ca

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