EUROPEAN JOURNAL OF Haematology

European Journal of Haematology 91 (62–68)

ORIGINAL ARTICLE

Clinical correlates of acute pulmonary events in children and adolescents with sickle cell disease*

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Abstract

Objectives: We aimed to identify risk factors for acute pulmonary events in children and adolescents in the Pulmonary Hypertension and the Hypoxic Response in SCD (PUSH) study. *Methods:* Patients with hemoglobin SS ($n = 376$) and other sickle cell genotypes ($n = 127$) aged 3–20 yrs were studied at four centers in a cross-sectional manner. A subgroup ($n = 293$) was followed for a median of 21 months (range 9–35). *Results:* A patient-reported history of one or more acute pulmonary events, either acute chest syndrome (ACS) or pneumonia, was obtained in 195 hemoglobin SS patients (52%) and 51 patients with other genotypes (40%). By logistic regression, history of acute pulmonary events was independently associated with patient-reported history of asthma ($P < 0.0001$), older age ($P = 0.001$), >3 severe pain episodes in the preceding 12 months ($P = 0.002$), higher tricuspid regurgitation velocity (TRV) ($P = 0.028$), and higher white blood cell (WBC) count ($P = 0.043$) among hemoglobin SS patients. History of acute pulmonary events was associated with >3 severe pain episodes ($P = 0.009$) among patients with other genotypes. During follow-up, 43 patients (15%) had at least one new ACS episode including 11 without a baseline history of acute pulmonary events. History of acute pulmonary events (odds ratio 5.0; $P < 0.0001$) and younger age (odds ratio 0.9; $P = 0.007$) were independently associated with developing a new episode during follow-up. *Conclusions:* Asthma history, frequent pain, and higher values for TRV and WBC count were independently associated with history of acute pulmonary events in hemoglobin SS patients and frequent pain was associated in those with other genotypes. Measures to reduce pain episodes and control asthma may help to decrease the incidence of acute pulmonary events in SCD.

Key words sickle cell disease; acute chest syndrome; vaso-occlusive crisis; asthma; pain

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*Supported in part by grant nos. 2 R25 HL003679-08 and 1 R01 HL079912-02 from NHLBI, by Howard University GCRC grant no 2MOI RR10284-10 from NCRR, NIH, Bethesda, MD, and by NIH intramural funding 1 ZIA HL006016-03.

Accepted for publication 3 April 2013

doi:10.1111/ejh.12118

Acute chest syndrome (ACS) is a frequent pulmonary complication of sickle cell disease (SCD) defined as an acute illness characterized by fever and/or respiratory symptoms accompanied by a new pulmonary infiltrate on a chest X-ray (1, 2). It is second only to vaso-occlusive crisis (VOC) as a cause of hospitalization and recurrent episodes may cause debilitating chronic pulmonary disease (3). It is also a leading cause of death in SCD, accounting for approximately 25% of deaths (4, 5). The cause of ACS is known in only about a third of cases and includes pneumonia, pulmonary infarction, and fat embolism. Other conditions that can precipitate ACS include general anesthesia and asthma (2, 6–8). The

pathogenesis of ACS is complex and is related to pulmonary vaso-occlusion and ischemia, airway inflammation, and endothelial dysfunction (9–11). The risk factors for predicting ACS are not clearly defined. In an analysis of the Cooperative Study of Sickle Cell Disease data, Castro *et al.* (2) described younger age, lower hemoglobin F, less severe anemia, and a higher steady-state leukocyte count as significant risk factors for ACS. In contrast, the only risk factor that predicted ACS in a Brazilian study reported by Araújo *et al.* (12) was a history of previous admission. Historically, half of all SCD patients had at least one episode of ACS in their lifetime and a subset had multiple events. Half of ACS episodes developed during hospitalization for another complication of SCD, most frequently VOC (5). In clinical practice, there is often overlap between the diagnoses of pneumonia and ACS in children with SCD. In this study, we report clinical factors associated with patient-reported history of ACS or pneumonia from analysis of data from a more recent cohort of children and adolescents with SCD.

Patients and methods

Study design and research participants

The Pulmonary Hypertension and the Hypoxic Response in SCD (PUSH) study is a prospective, multicenter study designed to determine the prevalence and risk factors of pulmonary hypertension in children and adolescents with SCD and to determine the role of the hypoxic response in its pathogenesis (13). PUSH enrolled participants with hemoglobin SS ($N = 376$) and other sickle cell disease genotypes ($N = 127$) 3–20 yrs of age as well as age- and gender-matched controls without SCD at four centers including Howard University and Children's National Medical Center in Washington, DC, the University of Michigan in Ann Arbor, Michigan, and the Pulmonary and Vascular Medicine Branch of the NHLBI, Bethesda, MD. The study protocol was approved by the institutional review boards of all participating institutions. Written informed consent to participate in the study was obtained from the subjects and/or their legal guardian. The study was performed in accordance with the Declaration of Helsinki and is registered with clinicaltrial.gov (NCT00495638). The patients were evaluated at steady state, defined as at least 3 wks after hospitalization for an acute vaso-occlusive crisis or other complication, with a detailed history and physical examination, laboratory tests, an echocardiogram, and pulmonary function tests (children ≥ 7 yrs). The present report includes all of the patients with sickle cell disease enrolled in the study and the subset that was evaluated after approximately 2 yrs of follow-up.

Participants were evaluated at enrollment, and a subset was followed prospectively for the occurrence of outcomes. Sickle cell disease genotype was confirmed by DNA sequencing, hemoglobin electrophoresis, and/or high-performance liquid chromatography. α-thalassemia genotyping was performed by assessing $-\alpha^{3.7}$ and $-\alpha^{4.2}$ thalassemia alleles. Hemoglobin concentration, leukocyte, platelet and reticulocyte counts, serum lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, ferritin, fetal hemoglobin percentage, and creatinine were measured at enrollment using standard methodologies. Transthoracic Doppler echocardiography was performed and used to estimate the systolic pulmonary artery pressure through measurement of the peak tricuspid regurgitation velocity (TRV). Left ventricular filling pressures were estimated by calculating the ratio of the mitral inflow E wave to the tissue Doppler E wave (E/Etdi) (14–16). History of the acute pulmonary events of ACS or pneumonia was obtained by interviewing parents, guardians, or patients and by reviewing the medical records for episodes diagnosed as ACS or pneumonia when available, but chest X-rays and the accompanying symptoms were not routinely reviewed. The number of severe VOC crises within the preceding 12 months was family- reported and included painful crises that required an emergency department or physician office visit or hospitalization. Histories of hydroxyurea use and blood transfusions were also obtained at enrollment and follow-up visits.

Statistical analysis

Continuous variables at recruitment were compared between patients with and without a history of acute pulmonary events with the Kruskal–Wallis test, and categorical variables were compared with the chi-square test. Independent predictors of history of ACS or pneumonia were assessed by logistic regression analysis. Variables that had P-value ≤ 0.2 in univariate analysis were entered into the final model. We also used logistic regression analysis to assess the predictors of new ACS during the follow-up period. Final multivariate models were built by the backward stepwise approach. Analyses were performed in STATA 12.0 (StataCorp, College Station, TX, USA).

Results

From 2006 to 2010, 503 participants aged 3–20 yrs were enrolled including 376 with hemoglobin SS and 127 with other SCD genotypes. We first analyzed baseline patient characteristics according to whether or not participants had a history of at least one acute pulmonary event as shown in Table 1. A history of ACS or pneumonia was present in 195 (52%) of hemoglobin SS patients and 51 (40%) of patients with other SCD genotypes ($P = 0.023$). Compared to those without such a history, hemoglobin SS patients with a history of acute pulmonary events at baseline were older, had significantly more severe pain episodes in the preceding 12 months, had received more blood transfusions, more often had a history of asthma, and had higher median WBC

Table 1 Patient characteristics according to history of acute pulmonary events. Results in median (IQ range) unless otherwise indicated

	N	Patients without ACS or pneumonia history	*N*	Patients with ACS or pneumonia history	*P*
a. Hb SS					
Age (yr)	181	11 (6–16)	195	13 (8–17)	0.0007
Female gender, no (%)	181	84 (46%)	195	97 (50%)	0.5
α-thalassemia					
Single deletion, no (%)	169	43 (25%)	178	62 (35%)	0.14
Double deletion, no (%)		5 (3%)		3 (2%)	
Hydroxyurea treatment, no (%)	181	74 (41%)	195	87 (45%)	0.5
History of chronic transfusion program, no. (%)	179	31 (17%)	193	34 (18%)	0.9
>3 severe pain episodes past year, no (%)	181	11 (6%)	195	46 (24%)	<0.0001
More than 10 blood transfusions, no (%)	178	39 (22%)	192	62 (32%)	0.025
History of asthma, no (%)	181	25 (14%)	195	71 (36%)	<0.0001
Hemoglobin (g/L)	174	86 (76–97)	188	87 (79–94)	>0.9
Reticulocyte count ($\times 10^9$/L)	166	246 (179–330)	183	265 (191–347)	0.16
WBC ($\times 10^9$/L)	173	10.7 (7.8–13.5)	188	11.4 (9.1–13.8)	0.032
Platelets ($\times 10^9$/L)	173	396 (318–484)	188	399 (333–503)	0.2
LDH (U/L)	158	462 (349–589)	167	438 (331–587)	0.3
Creatinine (μmol/L)	172	35.4 (26.5–44.2)	188	35.4 (26.5–44.2)	0.18
Ferritin (μg/L)	148	169 (79–626)	164	348 (129–1144)	0.001
TRV (m/s)	155	2.3 (2.1–2.4)	179	2.4 (2.2–2.5)	0.015
Mitral valve E/Etdi	167	6.7 (5.7–7.5)	184	6.4 (5.6–7.6)	0.7
b. Other genotypes (hemoglobin SC, $n = 88$; hemoglobin Sβ^+-thalassemia, $n = 21$, hemoglobin Sβ^0-thalassemia, $n = 12$; other, $n = 6$)					
Age (yr)	76	11 (7–15)	51	11 (7–15)	0.4
Female gender, no (%)	76	37 (49%)	51	26 (51%)	0.8
α-thalassemia					
Single deletion, no (%)	75	19 (25%)	49	26 (33%)	0.4
Double deletion, no (%)		5 (7%)		1 (2%)	
Hydroxyurea treatment, no (%)	76	9 (12%)	51	16 (31%)	0.007
History of chronic transfusion program, no. (%)	75	2 (3%)	51	4 (8%)	0.18
>3 severe pain episodes past yr, no (%)	76	2 (3%)	51	11 (22%)	0.001
More than 10 blood transfusions, no (%)	76	3 (4%)	51	5 (10%)	0.18
History of asthma, no (%)	76	13 (17%)	51	13 (25%)	0.3
Hemoglobin (mg/dL)	75	110 (100–117)	49	109 (100–116)	0.8
Reticulocyte count ($\times 10^9$/L)	73	147 (115–178)	47	140 (120–176)	0.7
WBC ($\times 10^9$/L)	75	7.7 (6.1–10.0)	50	7.3 (5.7–9.5)	0.8
Platelet ($\times 10^9$/L)	75	263 (190–397)	50	285 (193–354)	0.5
LDH (U/L)	72	274 (214–354)	46	284 (232–375)	0.4
Creatinine (μmol/L)	76	44.2 (35.4–61.9)	47	44.2 (35.4–53.0)	>0.9
Ferritin (μg/L)	66	105 (54–205)	43	136 (71–375)	0.10
TRV (m/s)	72	2.2 (2.0–2.3)	42	2.1 (2.0–2.4)	0.6
Mitral valve E/Etdi	75	6.1 (5.4–7.0)	46	5.9 (5.3–6.8)	0.4

ACS, acute chest syndrome; LDH, lactate dehydrogenase; TRV, tricuspid regurgitation velocity; WBC, white blood cells.

counts, serum ferritin concentrations and TRVs. There was no significant difference in gender, α-thalassemia status, hydroxyurea use, reticulocyte count, LDH, or mitral valve E/Etdi. In other SCD genotypes, those with a history of acute pulmonary events were more often receiving hydroxyurea and had a higher frequency of severe pain episodes.

We next examined which baseline variables were independently associated with history of acute pulmonary events using a logistic regression model (Table 2). History of asthma, older age, number of severe pain episodes in the previous year, TRV, and WBC count were independently associated with history of ACS or pneumonia in patients with hemoglobin SS. Number of severe pain episodes in the previous year and hydroxyurea therapy had significant independent associations with a history of these acute pulmonary events in SCD patients with other genotypes.

It can be difficult to adequately evaluate the influence of hydroxyurea treatment on risk factors for acute pulmonary events in SCD. History of acute chest syndrome is an indication for hydroxyurea but the treatment, once started for a different complication such as frequent severe pain episodes, may in turn prevent the development of acute pulmonary events. A chronic transfusion program can also complicate the interpretation of cross-sectional data. We therefore

Table 2 Independent predictors of history of ACS or pneumonia from multiple logistic regression modeling

	OR (95% CI)	*P*-value
a. Hb SS (n = 318)[1]		
History of asthma	3.9 (2.1–7.3)	<0.0001
Age (yrs)	1.09 (1.03–1.14)	0.001
>3 severe pain episodes in last year	4.4 (1.9–10.1)	0.002
TRV (m/s)	3.2 (1.1–9.1)	0.028
WBC (natural log)	2.03 (1.02–4.01)	0.043
b. Other genotypes (N = 127)[2]		
>3 severe pain episodes in last year	8.35 (1.72–40.58)	0.009
Hydroxyurea treatment	2.76 (1.06–7.23)	0.038

ACS, acute chest syndrome; LDH, lactate dehydrogenase.
[1]Variables entered into model: age, α-thalassemia status, number of blood transfusions, category of severe pain episodes, history of asthma, reticulocyte number, platelets, WBC count, ferritin, LDH, TRV. Four outliers were removed.
[2]Variables entered into model: hydroxyurea treatment, number of blood transfusions, number of severe pain episodes, ferritin.

examined the logistic regression models presented in Table 2 in patients not receiving hydroxyurea and not on a chronic transfusion program. Among 136 such hemoglobin SS patients, 70 had a history of acute pulmonary events; age (odds ratio 1.13, $P = 0.001$) and history of asthma (odds ratio 2.9, $P = 0.028$) had significant associations with this history while >3 severe pain episodes in the previous year (odds ratio 2.5, $P = 0.16$), TRV (odds ratio = 3.0, $P = 0.2$) and natural log WBC count (odds ratio 2.2, $P = 0.15$) had associations that no longer achieved statistical significance. Among 96 patients with other genotypes not receiving hydroxyurea and not on a chronic transfusion program, 32 had a history of acute pulmonary events; 100% of six patients with greater than three severe pain episodes in the previous year had this history compared to 29% of 90 patients with three or less severe pain episodes ($P = 0.001$).

Follow-up information was available for 293 participants (62%), including 214 with hemoglobin SS and 79 with other SCD genotypes, at a median of 21 months (range of 9–50 months). Forty-six percent had a history of ACS or pneumonia at baseline and 41% were being treated with hydroxyurea at baseline. The reasons for participants not having follow-up included recent hospitalization, failure to keep an appointment, failure to agree to follow-up, inability to make contact to schedule the follow-up, or end of grant funding. The children having follow-up did not differ significantly from those not having follow-up in terms of baseline history of asthma, history of severe pain episodes, hemoglobin concentration, and markers of hemolysis. During the follow-up period, 43 patients (15%) experienced ACS episodes, including 33 hemoglobin SS patients. Among patients with a history of acute pulmonary events at baseline, 25% had a new episode of ACS during follow-up while among 147 patients with no history of ACS or pneumonia, 7% had a new episode ($P < 0.0001$). Among patients receiving hydroxyurea at baseline, 18% had a new episode of ACS during follow-up while among patients not receiving hydroxyurea, 14% had a new episode ($P = 0.4$). Among all patients, a prior history of acute pulmonary events ($P < 0.0001$) and younger age ($P = 0.0007$) at baseline were significant predictors of ACS during follow-up, while baseline chronic transfusion program or hydroxyurea therapy were not significant predictors (Table 3).

Discussion

Understanding the risk factors for developing acute pulmonary events such as ACS in SCD may enable us to alleviate modifiable variables and potentially prevent ACS. In clinical practice, a distinction between pneumonia and ACS is often blurred; therefore, we used a broader definition of history of acute pulmonary events in the present study. We evaluated a large cohort of SCD patients at baseline and then re-evaluated more than half of them after approximately 2 yrs. In the cross-sectional analysis at baseline, a history of acute pulmonary events was independently associated with >3 severe pain episodes in the preceding year in hemoglobin SS patients and in patients with other genotypes. Additional associations with history of acute pulmonary events were found for history of asthma, older age, higher steady-state TRV, and higher WBC count in the hemoglobin SS patients. During the follow-up period, a baseline history of acute pulmonary events and younger age independently predicted new ACS episodes.

Our finding that coexistent asthma was associated with a history of acute pulmonary events is similar to previous reports (17, 18). Some investigators have reported that asthma is more common among children with SCD than

Table 3 Independent predictors of ACS during the follow-up (n = 273)

	OR (95% CI)	*P*-value
History of ACS or pneumonia at recruitment	5.0 (2.3–11.0)	<0.0001
Age (yrs)	0.91 (0.84–0.97)	0.007
Baseline chronic transfusion program	1.7 (0.7–4.4)	0.3
Baseline hydroxyurea treatment	1.4 (0.7–2.9)	0.4

ACS, acute chest syndrome; LDH, lactate dehydrogenase.
Variables entered into model include: genotype, age, gender, hydroxyurea treatment, number of blood transfusions, number of severe pain in last year, history of asthma, history of ACS or pneumonia at recruitment, hemoglobin, MCV, WBC (natural log), platelet (square root), LDH (natural log), ferritin (natural log), tricuspid regurgitation velocity, mitral valve E/Etdi. Hydroxyurea treatment and chronic transfusion program were forced into the model.
Area Under ROC Curve = 0.73, *P*-value for goodness of fit = 0.8.

ethnic matched controls (19). In contrast, a history of asthma is similar in SCD and control children in the PUSH study (13), and a recent review of a number of studies concluded that the prevalence of asthma in SCD is similar to or slightly higher than the general African–American population (20). However, bronchial hyper-responsiveness is more common in children with SCD than in ethnically matched controls, and atopic asthma appears to be associated with recurrent ACS (21, 22). Further research is needed to determine if aggressive control of asthma may decrease the risk of ACS in SCD patients.

Our finding that a history of >3 severe pain episodes in the preceding 12 months was associated with a history of acute pulmonary events is consistent with the clinical observation that severe painful crises often precede ACS. The mechanism may involve the development of hypoventilation and atelectasis from rib infarction (23, 24), excessive opioid administration (25, 26), or embolization of infarcted bone marrow to the lungs (7). The routine use of incentive spirometry to prevent atelectasis in the setting of acute vaso-occlusive pain crisis is effective in preventing ACS (23). The association of higher steady-state WBC count with ACS or pneumonia in hemoglobin SS patients in this study is consistent with an analysis of ACS in the Cooperative Study of Sickle Cell Disease (2).

The median steady-state TRV was 2.4 m/s in the hemoglobin SS children and adolescents in the present study with a history of an acute pulmonary event vs. 2.3 m/s in those without such a history, and both of these values are within the normal range. Nevertheless, higher TRV was independently associated with history of acute pulmonary events, and this is in contrast to several previous reports failing to find such an association in children (27–29) and adults (30). TRV elevation is common in SCD adults during an episode of acute chest syndrome (31). Elevated TRV is known to be a physiologic biomarker of severity in adult patients with SCD (30, 32, 33), but its prognostic significance in children is largely not known. We previously reported that elevated TRV in children is associated with a decline in exercise capacity over 2 yrs of follow-up (34). We are unable to make a conclusion as to whether the association between higher TRV and ACS or pneumonia in this study is causal.

A third of patients with a history of acute pulmonary events developed ACS during a median follow-up of 21 months in the present study. A study from the Dallas Newborn Cohort demonstrated that ACS in the first 3 yrs of life significantly increased the odds of more frequent episodes of ACS during childhood (6). Other studies indicate that acute chest syndrome or acute respiratory distress syndrome in childhood may lead to sequelae such as obstructive and/or restrictive abnormalities, fibrosis, and hypoxemia (35–37). Perhaps pulmonary injury from previous acute pulmonary events predisposes to increased susceptibility to recurrent events or alternatively a genetic predisposition underlies the development of frequent ACS episodes (38). Younger age was associated higher risk of ACS during the follow-up period in our study. This observation is consistent with other reports that ACS is more common in younger patients, with the highest incidence seen in children aged 9 yrs or less and the lowest incidence in adults (2). There is a higher risk of viral or bacterial infections in early childhood, and pulmonary infections are a frequent trigger of ACS (7). A decrease in the frequency of ACS episodes in individuals with age might be explained by acquired immunity and the preferential survival of children with a lower incidence of ACS. In general, the physiologic abnormalities of obstructive/restrictive defects on pulmonary function testing and hypoxemia are likely reflective of an ill-defined chronic lung injury that occurs in SCD and may predispose to recurrent episodes of ACS.

There are several limitations in our study. First, the diagnoses of acute chest syndrome, pneumonia, and asthma were reported by the patient or a family member and were not confirmed by chart review in all subjects. Second, associated genomic and genetic analyses would be helpful to clarify relevant biological mechanisms in the context of biochemical and historical risk markers. Third, the median follow-up of 21 months was short and may have limited the identification of potential beneficial effects of hydroxyurea treatment in SCD patients.

In conclusion, our data indicate that acute pulmonary events are frequent in both hemoglobin SS patients and those with other genotypes. History of frequent severe pain episodes was an independent predictor of a history of acute pulmonary events among all genotypes and history of asthma, higher TRV, and higher WBC count in patients with hemoglobin SS. Future research should investigate whether preventing severe pain episodes and providing optimal treatment for asthma will decrease the incidence of acute pulmonary events in children and adolescents with SCD. Furthermore, our results suggest the possible importance of stratifying ACS diagnosis according to accompanying findings such as asthma history, frequent acute pain episodes and increased estimated systolic pulmonary artery pressure for future studies of genotype–phenotype correlation.

Authorship and disclosure

RP, OA participated in statistical analysis and writing the paper. CPM, LLJ, AC, SR, OO, DD, MA, GE, GS, ND, GK, MG, OLC participated in data collection and writing the paper. MN performed statistical analysis and participated in writing the paper. VRG was the principle investigator and participated in statistical analysis and writing the paper. The authors do not have any conflict of interest to report.

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