Acute chest syndrome in sickle cell disease: Effect of genotype and asthma

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Abstract

Sickle cell disease is a severe hemoglobinopathy caused by mutations in the beta globin genes. The disorder has protean manifestations and leads to severe morbidity and early mortality. Acute chest syndrome (ACS) is a common complication and in the USA is the leading cause of death in patients with sickle cell disease. Care of patients with sickle cell disease is complex and typically involves both primary care physicians and hematology subspecialists. The purpose of this study was first to attempt to validate in a pediatric sickle cell patient cohort associations between ACS and sickle cell disease genotype and between ACS and asthma as a comorbidity. The second purpose of the study was to study in a typical community the frequency with which asthma associated with ACS was addressed in terms of electronic medical record integration, pulmonary subspecialty consultation for management of asthma, and completion of pulmonary function testing (PFTs). A retrospective study of the electronic medical record of a children's hospital that provides most of the medical care for children in a portion of western New York state was performed. We found that ACS was more common in the sickle cell disease genotypes SS and S/beta-thalassemia-null, and that ACS was more frequent in patients treated for asthma. We also found that despite the use of a comprehensive electronic medical record, there was poor documentation of ACS and asthma episodes in the problem lists of patients with sickle cell disease, and that most patients with sickle cell disease with ACS or asthma failed to receive formal consultation services from pediatric pulmonary subspecialists.

Keywords: Sickle cell disease, hemoglobinopathy, pulmonary function, acute chest syndrome, asthma, hematology

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Introduction

Sickle cell disease is a severe hemoglobinopathy caused by mutations in the beta globin genes. The disorder has protean manifestations and leads to severe morbidity and early mortality.^{1,2} Normal adult hemoglobin is composed of two alpha and two beta chains, and mutation in the beta chain results in sickle cell disease (SCD). SCD comprises a spectrum of genotypes including homozygous sickle cell anemia (HgbSS), hemoglobin SC disease (HgbSC), hemoglobin sickle-beta thalassemia positive (HgbS-beta-thalassemia-plus), and hemoglobin sickle-beta thalassemia null (HgbS-beta-thalassemia-null). In individuals carrying beta thalassemia genes in addition to hemoglobin S, beta chain production is either reduced (HgbS-beta-thalassemia-plus) or absent (HgbS-beta-thalassemia-null). The result of the above defects is a dysfunctional red blood cell with a shortened life span, leading to a wide range of clinical complications. Phenotypic presentations of SCD vary greatly, but in general individuals with HgbSS and HgbS-beta-thalassemia-null have more severe courses.

While vaso-occlusive crisis leading to pain is the most common manifestation of the disease, acute chest syndrome (ACS)³ is the leading cause of premature death, and the second most common reason for hospitalization. ACS is typically defined as the presence of a new infiltrate on chest radiograph in addition to one of the following symptoms: fever, chest pain, shortness of breath, hypoxia, or tachypnea. The most common cause of ACS is infection, usually triggered by bacteria or viruses. Fat embolization and pulmonary infarction can lead to ACS as well, but these are more common etiologies in the adult population.

In the past decade, there have been several reports linking ACS and asthma in patients with SCD.^{4–8} The presence of asthma in SCD has been associated with increased risk of developing ACS. In addition, the first ACS event tends to occur at a younger age when compared to patients who do not have asthma. The pathophysiological mechanism for such an association between ACS and asthma is not yet fully known. Some hypothesize that obstruction of lung segments by inflammation leads to ventilation and perfusion

mismatching causing local hypoxia and thus sickling of red blood cells.

In many communities, the medical care of children with SCD is generally directed by general pediatricians or family practice physicians, with pediatric hematologists managing acute episodes of sickle cell complications in hospital and seeing children two to four times yearly for sickle cell-specific health issues. Asthma is a common condition in general pediatrics and is typically managed by pediatricians.

One purpose of this study was to examine the relationship between the frequency of ACS in patients with SCD and (i) the genotype of the SCD, and (ii) the comorbid condition of wheezing or asthma. The second purpose of the study was to study in a typical community the frequency with which asthma associated with ACS was addressed in terms of electronic medical record integration, pulmonary subspecialty consultation for management of asthma, and completion of pulmonary function testing (PFTs).

Methods

This study was a retrospective electronic medical record review of patients receiving hematology subspecialty care in the Division of Pediatric Hematology/Oncology at the University of Rochester Medical Center. A total of 102 patients were included in the study with the electronic medical records including the era of 2005–2014. Inclusion criteria included patients from 2 to 21 years of age with a diagnosis of Hemoglobin SS, Hemoglobin SC, Hemoglobin S-beta-thalassemia-plus, or Hemoglobin S-beta-thalassemia-null. Patients were considered to have asthma if they had a physician-assigned diagnosis or if they had received outpatient treatment with albuterol and/or inhaled corticosteroids. Data regarding gender, age, type of SCD, diagnosis of asthma, PFT completion, presence or absence of pulmonary consult, and number of ACS episodes were collected. ACS was defined as the presence of a new pulmonary infiltrate plus one or more associated symptoms of either: fever, chest pain, hypoxia, tachypnea, or shortness of breath. Patients were excluded if there were significant gaps in time in their medical record prohibiting accurate analysis of their asthma and/or ACS history.

Table 1 Sickle cell genotype affects probability of acute chest syndrome

Genotype	Acute Chest Syndrome	
	No	Yes
SS	25	26
SC	25	12
S-beta thalassemia plus	10	1
S-beta thalassemia null	2	1
Total	62	40
<i>Chi square overall $p = 0.048$</i>		
SS or S-beta thalassemia null	27	27
SC or S-beta thalassemia plus	35	13
<i>Chi square $p = 0.031$</i>		

Results

Of the 102 patients with SCD, 40 had one or more episodes of ACS (39%). The incidence of ACS varied with the genotype of SCD. Fifty percent of patients with HgbSS or HgbS-beta-thalassemia-null genotypes had episodes of ACS, while only 27% of patients with HgbSC or HgbS-beta-thalassemia-plus had any episodes of ACS (Table 1, $P = 0.03$).

Of the 102 patients studied, 29 patients had been treated for asthma (28%). By comparison, the Center for Disease Control reports that among US children, the prevalence of asthma is 8.3% (<http://www.cdc.gov/asthma/asthma-data.htm>). We observed a strong relationship between asthma and ACS (Table 2). Among the 73 patients who were never treated for asthma, we observed that only 17 (23%) had experienced at least one episode of ACS. In contrast, 23 of the 29 patients treated for asthma experienced ACS (79%, $P < 0.00001$). We further asked whether patients treated for asthma had experienced more than one episode of ACS (Table 2). It was found that 14 of these 29 patients treated at some time for asthma experienced 2 or more episodes of ACS (48%). In contrast, only 9 of 73 patients not treated for asthma had two or more episodes of ACS (12%, $P = 0.0003$).

We further examined the relationship between asthma and ACS in the sickle SC genotype group. Even in this group in which ACS was less common, we observed that 75% (9 of 12) SC patients who suffered ACS also had a diagnosis of asthma, compared to 12% (3 of 25) among those SC patients who never experienced ACS ($P = 0.0005$). In comparison, 54% (14 of 26) genotype SS patients who suffered ACS had a diagnosis of asthma, compared to 8% (2 of 25) genotype SS patients who never had an episode of ACS ($P = 0.0012$).

Electronic medical record systems contain a problem list section in which active and resolved medical conditions are listed, and their purpose is to quickly and efficiently communicate to those caring for a patient the most important parts of the patient's medical history. We examined these lists for conditions of ACS or asthma, and compared these with the information that was manually extracted from clinic and hospital notes (Table 3). Surprisingly, we found significant gaps in the problem lists. Among the 40 patients

Table 2 Acute chest syndrome is more common in sickle cell patients with asthma

Asthma	Acute Chest Syndrome	
	No	Yes
Yes	6	23
No	56	17
<i>Chi squared $p < 0.00001$</i>		
Asthma	Number of ACS Episodes	
	0 or 1	2 or more
Yes	15	14
No	64	9
<i>Chi squared $p = 0.0003$</i>		

Table 3 Documentation of pulmonary complications and subspecialty care in patients with sickle cell disease

Diagnosis		Diagnosis in EMR		PFTs Done		Pulmonary Consult	
		Yes	No	Yes	No	Yes	No
ACS	Yes	23	17	12	28	6	34
	No	0	64	7	57	0	64
Asthma	Yes	20	9	8	21	6	23
	No	0	73	11	62	0	73
ACS & Asthma		12	11	8	15	6	17

treated for ACS, 17 (42%) did not have the episodes documented in the problem list. Of the 29 patients treated for asthma, nine (31%) did not have asthma in the problem list. Twenty-three patients had been treated for both ACS and asthma; among these only 12 (52%) had both problems documented in the problem list.

Given the association of asthma and ACS, we measured the frequency with which these patients received formal pulmonary function testing and/or pulmonary subspecialty consultation. Of the patients with asthma, 8 of 29 (28%) had PFTs completed and 6 of 29 (21%) had a formal pulmonary consult (Table 3). Of the patients with a diagnosis of ACS, 12 of 40 (30%) had PFTs completed and 6 of 40 (15%) had a pulmonary consult. In patients with both ACS and asthma, 8 of 23 (35%) had PFTs completed and 6 of 23 (26%) had a formal pulmonary consult.

Discussion

This retrospective study of ACS and asthma in pediatric patients with SCD confirmed previous observations regarding the relationship between the two. All sickle cell genotypes are at risk for ACS, but patients with HgbSS or HgbS-beta-thalassemia-null genotypes are at the highest risk. We also confirmed that patients treated for asthma are also much more likely to experience episodes of ACS.

Our findings of the relationship between asthma and ACS are in harmony with a number of reports in the past decade. Knight-Madden *et al.*⁴ reported that children with sickle cell disease were more than twice as likely to have asthma or bronchial hyperreactivity, and that asthma was more common in children who had suffered recurrent episodes of ACS. Boyd *et al.*⁵ reported from the Cooperative Study for Sickle Cell Disease that the frequency of ACS events was twice as high in patients with a diagnosis of asthma. Duckworth *et al.*⁶ reported a relationship between physician-diagnosed asthma and ACS. Paul *et al.*⁷ in the Pulmonary Hypertension and Hypoxic Response in SCD (PUSH) study found that acute pulmonary events (ACS or pneumonia) were statistically associated with asthma history, frequent pain episodes, abnormal tricuspid regurgitation velocity and WBC. DeBaun *et al.*⁸ reported observations from the multicenter Sickle Cell Cohort study and noted that specific features of asthma were related to future episodes of ACS. These features included an episode of ACS before the age of 4 years, wheezing causing shortness of breath, and multiple positive skin tests for atopy.

Although we observed that that ACS is less common in patients with the SC genotype, within the SC patients there was still a strong relationship between asthma and ACS. This is similar to the report of Poulter *et al.*⁹ who concluded that while ACS may be less severe in SC disease, wheezing and asthma remain significant risk factors.

Asthma is a common condition in childhood. It is routinely managed by primary care pediatricians and family physicians without formal pulmonary medicine consultation or formal PFTs. The NIH guidelines on asthma are a tool for physicians to understand the diagnosis, necessary follow-up, and management of asthma (<http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines>). These guidelines define asthma based on four distinct categories: intermittent asthma, mild persistent, moderate persistent, and severe persistent. These categories are based on frequency of both daytime and nighttime symptoms, interference with normal daily activities, and PFT data. Depending on the severity of asthma, management and escalation of treatment is clearly defined in order to achieve optimal asthma control. As outlined in the NIH asthma guidelines, PFTs are a necessary objective measure to demonstrate airway obstruction to aid in the diagnosis of asthma, and are essential in monitoring response to controller medication and thus optimizing asthma management.

We did not observe any sickle cell disease-related mortality (pulmonary or nonpulmonary) in our cohort of pediatric patients. This probably represents successful implementation of sickle cell disease standard of care guidelines. However, it is still very likely that patients are experiencing cumulative chronic organ damage. Santoli *et al.*¹⁰ reported more obstructive lung dysfunction in sickle cell patients who had experienced ACS. Arteta *et al.*¹¹ reported that 19% of children with sickle cell SS or S-beta-thalassemia null genotypes had abnormal pulmonary function tests. This may translate into increased risk of death in adulthood in patients with sickle cell disease. Boyd *et al.*¹² reporting from the Cooperative Study for Sickle Cell Disease that included nearly 2000 patients observed significantly increased mortality rates among sickle cell disease patients with asthma starting in late adolescence and young adulthood. Cohen *et al.*¹³ reported increased mortality in adult sickle cell patients with recurrent, severe wheezing episodes. Knight-Madden *et al.*¹⁴ studied a group of young adults with sickle cell disease and observed a substantially higher mortality rate in those patients with either asthma or smoking.

Given the high risk nature of patients with SCD and asthma, PFT completion would aid in proper categorization

of asthma status, and consultation with a pediatric pulmonologist will ensure optimal disease management. Previous studies conducted in children with asthma have shown decreased hospitalization rates following pediatric pulmonary consultation, likely because of improved assessment of asthma severity and increased education and use of controller medications.¹⁵ While no specific studies have addressed this in the pediatric SCD population, it is reasonable to conclude that children with asthma and SCD would observe this same benefit in disease outcome. Our data show that a significant number of patients with SCD and asthma have not had PFTs completed, and an even larger proportion of them have not had a pediatric pulmonologist involved in their care. Further studies are needed in order to determine if morbidity and mortality are decreased with pulmonologist involvement in children with SCD and asthma. While one of the potential advantages of an electronic medical record is its intrinsic capacity to pull together large quantities of clinical data, our experience suggests that this capacity does not ensure efficient sharing of critical information throughout a system in which a number of physician groups participate in the care of a patient. Indeed, with many people responsible for assigning diagnoses and placing clinical information in the electronic record, there is a risk that no single individual is responsible for curating and organizing this information. This likely reflects the model of care in which various physicians are involved in the care of children with SCD resulting in some fragmentation of care.

This study does have its limitations. Given that it was a retrospective chart review, it does not represent a well-organized body of information that was uniformly collected on each patient over time. Given the well-described criteria for ACS, we are fairly confident on the identification of the episodes of ACS. In contrast, the diagnosis of asthma in patients is problematic. No uniform criteria are shared among physicians in making the diagnosis, and the clinical nature of the diagnosis raises the possibility that some patients with wheezing not due to asthma were placed into the "asthma category." We did try to minimize this likelihood by excluding patients under the age of 2, in which an asthma diagnosis is difficult given the frequency of wheezing with viral illness. A further concern is that in some cases the diagnosis of asthma may be more likely to be made in a patient who has experienced ACS. Our data do not allow us to sort this out, and if this was common it would lead to overestimation of the relationship between ACS and asthma.

Nonetheless, the study is a faithful "real world" picture of the related problems of asthma and ACS, and does point out several areas in which improvements in care of sickle cell patients could occur. The first is in creating and publicizing for both primary care physicians and hematologists of the increased risk of ACS in sickle cell disease, especially in those individuals with HgbSS and HgbS beta-thalassemia-null subtypes. The second possibility is the development of software algorithms that could be deployed in electronic medical records that could prompt both primary care and subspecialist physicians to more thoroughly evaluate sickle cell patients for asthma and attempt to optimize its treatment to reduce the risk of episodes of ACS.

Author's Contributions: KP formulated the hypothesis, designed the project, and collected the data. KP and CAM both analyzed the data, wrote the manuscript, and were involved in its editing.

DECLARATION OF CONFLICTING INTERESTS

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