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The Impact of the 2009 H1N1 Influenza Pandemic on Pediatric Patients With Sickle Cell Disease

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Abstract

Background—Respiratory infections are associated with clinically significant illness in patients with sickle cell disease (SCD). The 2009 H1N1 pandemic was perceived as a significant threat to this population.

Methods—We undertook a chart review of all patients with SCD followed at our institution to identify those with confirmed H1N1 infection. Further chart and laboratory data was collected on affected patients to analyze clinical courses and the factors that correlated with disease severity.

Results—Approximately half of the patients with confirmed H1N1 infection were managed successfully on an outpatient basis with oseltamivir therapy. Among the patients admitted, the most common diagnosis was acute chest syndrome (ACS). Most admitted patients had uncomplicated clinical courses, with a median length of admission of 3 days and no mortality or requirement for mechanical ventilation. A past history of ACS or reactive airway disease correlated with a higher rate of admission and of ACS incidence during the acute illness. Chronic transfusion therapy or hydroxyurea therapy with high hemoglobin F levels had a strong inverse correlation with incidence of ACS.

Conclusions—Our results indicate that that in general the impact of the H1N1 influenza pandemic on patients with SCD was mild but that past clinical history correlated with the severity of illness. Additionally, effective hydroxyurea therapy and chronic transfusion therapy appeared to be protective against the incidence of ACS. Our results suggest guidelines for the management of patients with SCD during future influenza pandemics as well as during seasonal influenza epidemics.

Keywords

hemoglobinopathies; infections; sickle cell disease

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INTRODUCTION

Sickle cell disease (SCD) is a genetic disorder resulting from a missense mutation in the beta chain of the hemoglobin molecule. While the unifying pathogenetic abnormality in SCD is the polymerization of sickle hemoglobin under hypoxic conditions with resultant erythrocyte deformation and destruction, the end-organ damage associated with the disorder is widespread and highly variable in severity [1]. Among the organ systems affected by SCD are the central nervous system, the lungs, the kidneys, bone, and the reticuloendothelial system [2]. In developed countries, the second most common cause of hospitalization and the most common cause of mortality among patients with SCD is acute pulmonary disease of various etiologies classified under the rubric of acute chest syndrome (ACS) [3–5]. ACS is defined as a new infiltrate on chest radiograph with accompanying fever, tachypnea, hypoxia, cough, or other evidence of respiratory distress. There are numerous causes of ACS, among them pulmonary infarction, bone marrow emboli, and infection by viruses, atypical organisms, and the bacteria associated with community-associated pneumonia.

Upper and lower airway infections are thought to pose a risk of triggering ACS in sickle cell patients. In particular, patients with SCD are considered to be at increased risk of complications from seasonal influenza epidemics, and the CDC has targeted this group of patients as a high-risk target population for influenza vaccination. A recent study of the influenza-associated hospitalization rate and complications among pediatric SCD patients supports this designation; children with SCD were 56 times as likely as non-SCD children to be hospitalized for influenza, although the duration of hospital stay and the severity of illness among those hospitalized was not significantly different between the two group [6]. Interestingly, there have been few other case reports on this subject or guidelines for the clinical management of influenza in patients with SCD.

In April 2009, a new variant of the influenza A virus, designated H1N1, was identified in Mexico and California, with subsequent spread worldwide [7]. Certain comorbid conditions, among them pregnancy, obesity, neurological disorders, and immunosuppression, have been identified as conferring an increased risk of severe disease or death from H1N1 infection [7]. Other risk factors for severe seasonal influenza illness, among them hemoglobinopathies such as SCD, are also presumed to confer increased risk of complicated H1N1 disease. There has, however, been limited data published to date describing the impact of the H1N1 pandemic on patients with SCD. One analysis of pediatric patients with SCD in London, England described 21 cases of PCR-confirmed H1N1 infection, with 19 being admitted and 10 developing ACS; the authors estimated an overall admission rate of 50% and an incidence rate of 25% for ACS [8]. Another report of 10 pediatric SCD patients with confirmed H1N1 influenza in Baltimore, MD described an 86% admission rate, a 34% incidence of ACS and a 10% requirement for mechanical ventilation. The risk of ACS with H1N1 infection was estimated at almost threefold that associated with prior seasonal influenza epidemics [9]. These preliminary reports suggested that H1N1 influenza poses a greater risk of complicated illness in patients with SCD.

In this report, we present a retrospective analysis of 48 patients with PCR-confirmed H1N1 or influenza A infection at our institution. While we did see a significant incidence of ACS, the patients described in this study had a lower admission rate than in the series described above, relatively brief hospital stays and generally uncomplicated courses. Our study represents the largest series to date of pediatric SCD patients with H1N1 influenza and suggests therapeutic guidelines for the management of this population of patients during further such pandemics as well as during seasonal influenza epidemics.

METHODS

This retrospective chart review study of the incidence of H1N1 influenza among patients with SCD was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center (CCHMC) prior to initiation. The electronic records of the 272 patients with all forms of SCD followed at the CCHMC Comprehensive Sickle Cell Center were reviewed for the period between September 2009 and March 2010 to identify all patients who had been tested for H1N1 or influenza A infection by viral RNA RT-PCR. As over 90% of all influenza A cases diagnosed at CCHMC during this period were positive when subsequently tested for the H1N1 strain, patients diagnosed with influenza A but without subsequent testing for H1N1 were included in our analysis of H1N1 cases. Demographic information, past history, and clinical and laboratory data related to the diagnosis of influenza were collected using a standardized data sheet. The charts of patients with confirmed H1N1 or influenza A infection were reviewed in more detail to identify presenting symptoms and signs, laboratory and radiological results, therapeutic interventions, hospital admission status, and the course of the hospital stay among admitted patients.

We used contingency tables with Chi square, Fisher's exact, or Cochran–Mantel–Haenszel test to determine the statistical significance of differences between sub-groups of patients for categorical variables. The unpaired *t*-test or Wilcoxon rank sum testing were used to compare means of continuous variables between groups. Due to small sample size, patients with SE, $S\beta^0$ thalassemia, and $S\beta^+$ thalassemia were collapsed into a single category for statistical analysis. Additionally, due to small sample size, patients who were on hydroxyurea therapy or chronic transfusion therapy were grouped together for analysis. Patients on hydroxyurea or chronic transfusion were categorized as strongly therapy-responsive (defined as having a hemoglobin F level over 30% for patients on hydroxyurea and as having a hemoglobin S level below 30% for patients on chronic transfusion) or less responsive for purposes of statistical analysis of the effects of these therapies on the rate of admission and incidence of ACS.

RESULTS

Patients with sickle cell disease who required evaluation in the Hematology clinic or the Emergency Department (ED) for febrile illness during the H1N1 pandemic were managed following Sickle Cell Disease Care Consortium guidelines [10]. Criteria for admission included age less than 6 months, history of pneumococcal sepsis or splenectomy, fever over 408C, toxic appearance or dehydration, chest infiltrates, oxygen requirement, significantly abnormal CBC parameters, or concurrent severe pain. The decision to admit or not from the

ED was made in consultation with the hematologist on call, and admitted patients were managed following standardized consortium guidelines. The decisions to test for influenza and to initiate oseltamivir therapy presumptively prior to test results were based on CDC guidelines issued during the pandemic [11]. These guidelines were utilized without modification throughout the 2009 H1N1 pandemic.

From the 272 patients whose charts were examined, 35 cases of H1N1 influenza and thirteen of influenza A were identified. In all cases, the diagnosis was made by virus-specific RT-PCR from nasal swabs or washes. There was no detectable difference in history, presenting symptoms, or clinical course between those positive for H1N1 influenza and those positive for influenza A (data not shown). The first case was diagnosed in early September, peak incidence of new cases was in mid-October, and the last case was in early December, corresponding to the overall pattern of incidence of H1N1 influenza among all patients tested at our institution. Male and female patients were equally represented among affected patients and SS patients were slightly over-represented relative to their frequency in the patient population, but this difference was not statistically significant (Table I). Thirteen of the affected patients were on hydroxyurea therapy, seven were on chronic transfusion therapy, and one was in the process of transition from chronic transfusion to hydroxyurea therapy. The most common symptoms at presentation were fever (92%), cough (77%), and congestion or rhinorrhoea (56%). Other relatively frequent symptoms included headache and myalgia (19%). Less common were abdominal pain, emesis, shortness of breath, wheezing, or malaise (4–8%).

Of the 48 patients with confirmed diagnoses, 45 were started on a 5-day course of oseltamivir, either empirically at initial evaluation or once the diagnosis of influenza was confirmed, and 43 received a dose of ceftriaxone during initial evaluation. Two were also prescribed a 5-day course of azithromycin for suspected occult pneumonia. Of the 27 patients initially treated on an outpatient basis, two were subsequently admitted, one because of delayed development of ACS after failing to initiate prescribed oseltamivir therapy and the other for a blood culture that became positive after initial evaluation despite absence of clinical symptoms or signs of bacteremia. The remaining 25 had no documented complications as outpatients. Twenty-three patients (48%) were admitted to the inpatient Hematology service for a variety of reasons. The most common diagnosis at admission was ACS, which was present in 10 patients (21% of the 48 affected patients). Other common reasons for admission included hypoxia without infiltrates on chest X-ray, seen in three patients, and dehydration, also present in three patients. Pain crises occurred in two patients, while one had splenic sequestration. As mentioned above, one patient had a blood culture that became positive for non-typeable *Streptococcus* species and was admitted for treatment of presumed bacteremia, although he was clinically well and repeat cultures were negative. Other reasons for admission included a small asymptomatic apical pneumothorax of uncertain etiology, paroxysmal and painful coughing, significant but non-focal myalgia, and factitious thrombocytopenia due to a laboratory error.

Of the 23 patients admitted to the inpatient service, most had a relatively uncomplicated course. All were started on empiric antibiotic coverage for 24–48 hr pending negative blood cultures, and thirteen patients with ACS or suspected occult pneumonia were prescribed a 5-

day course of azithromycin as well. All but one were also started on a 5-day course of oseltamivir. Five patients were placed on longer courses of IV antibiotics (ceftriaxone or vancomycin), four for persistent chest infiltrates and one for bacteremia. Nine of the 10 patients admitted with ACS received an RBC transfusion within 24 hr of admission, as did two of the three patients with hypoxia. (The two untransfused patients had hemoglobin concentrations over 10 mg/dl at admission). The patient with the apical pneumothorax had no respiratory compromise and had spontaneous resolution of the pneumothorax within 48 hr. The mean duration of hospitalization was 3 days. One patient required hospitalization for 8 days because of prolonged pain crisis and exacerbation of reactive airway disease, and one required transfer to the intensive care unit for exchange transfusion due to persistent hypoxia and worsening lung infiltrates after two simple transfusions, for a total hospitalization of 8 days. No patients required mechanical ventilation, and there was no mortality. A review of the period after discharge revealed no readmissions and no new requirement for bronchodilator therapy, increased chronic pain, or other immediate sequelae.

As a control group, sickle cell patients who had negative testing for H1N1 influenza during the same time period were also analyzed for patient characteristics, admission rates, and incidence of ACS. A total of 49 patients who had negative testing were identified. Since some of these patients were tested more than once, the total number of negative tests was 64. Comparison of this control group with H1N1-positive patients revealed was no significant difference in age, gender, distribution of sickle cell genotypes, admission rate, incidence of ACS, or duration of admission between the two groups (Table II). The H1N1-positive group had a significantly greater proportion of patients on hydroxyurea or chronic transfusion therapy, but the admission rate and rate of incidence of ACS did not differ between H1N1-positive and H1N1-negative patients on HU or chronic transfusion (data not shown).

In an effort to identify factors that might have predicted which patients with H1N1 influenza were at risk of more severe illness, we analyzed all 48 diagnosed patients for admission rate and rate of incidence of ACS stratified by age, gender, genotype, a concurrent diagnosis of reactive airway disease (RAD), and histories of frequent pain crises, ACS, splenic sequestration, and influenza immunization status (Table III). The mean and median ages of admitted patients were higher than those of patients not admitted but this difference was not statistically significant. There was also no significant difference between the ages of patients who developed ACS and those who did not. While male patients were somewhat more likely than females to be admitted and to develop ACS, these differences were not statistically significant. SS patients had a statistically non-significant higher admission rate than SC patients, and both groups of patients were equally likely to develop ACS. None of our patients had received the H1N1 influenza vaccine prior to diagnosis due to a lack of availability, but 17 had received the seasonal influenza vaccine. The rate of admission and of ACS incidence did not differ significantly between vaccinated patients and those who had not received the vaccine prior to contracting H1N1 influenza.

A history of past ACS or of reactive airway disease (RAD) was associated with increased admission rate and likelihood of ACS during the acute illness (Table III). Patients with RAD had higher rates of admission and of ACS incidence than those without RAD, with both differences approaching statistical significance. Patients with any past history of ACS had a

significantly higher admission rate and of incidence of ACS than those without past episodes of ACS. An episode of ACS within 12 months prior to the diagnosis of H1N1 influenza was especially strongly associated with admission and ACS. In contrast, a prior history of pain crises requiring hospitalization correlated with a higher rate of admission but not with a high incidence of ACS. Our sample size was too small to permit multivariate analysis, but of the five patients with a dual history of past ACS and RAD, all were admitted at diagnosis and three developed ACS. Additionally both patients who required prolonged hospitalization, one for complicated ACS and one for RAD exacerbation, belonged to this group.

We also analyzed severity of illness stratified by chronic therapy for SCD (Table IV). Patients on chronic transfusion had a high admission rate but no incidence of ACS. Among patients on hydroxyurea therapy, the mean HbF level was significantly lower among those who were admitted. Similarly, mean HbF was significantly lower among patients who developed ACS while on HU. Overall, patients who were strongly responsive to hydroxyurea or who were on chronic transfusion therapy had a lower, albeit non-significant, rate of admission than those who were less responsive to HU or on no chronic therapy (Table V). Strikingly, patients strongly responsive to HU (HbF > 30%) or on chronic transfusion had no incidence of ACS, a significant difference from all other patients diagnosed with H1N1 influenza (Table V). To determine whether lower levels of HbF might be protective against ACS or illness requiring admission, we also stratified patients on HU therapy into those with HbF over 20% (n = 10) and those under 20% (n = 4). Of the 10 patients with HbF levels over 20%, four required admission and only one developed ACS. Conversely, all four patients with HbF levels below 20% required admission and three developed ACS, although the differences between the groups was not statistically significant (data not shown).

DISCUSSION

In this report, we describe the impact of the 2009 H1N1 influenza pandemic on patients with SCD followed at our institution. In general terms, the effect of the pandemic on our SCD population was mild. While approximately 15% of our patients were diagnosed with H1N1 influenza and almost 50% of these affected patients required admission, most admitted patients had uncomplicated courses and brief hospital stays. The overall incidence of ACS was 21%, but only one patient required ICU admission for exchange transfusion, and none required mechanical ventilatory support. Additionally, most patients managed on an outpatient basis had no complications. Our findings are consistent with reports on the overall impact of the H1N1 pandemic indicating that the disease was milder than expected in the general population [7] but differ significantly from a prior report on its impact on patients with SCD, which described a significantly higher rate of ACS of 34%, with 10% of all patients requiring ventilatory support [8]. Additionally, there appeared to be no significant difference in patient characteristics or clinical course between patients evaluated for H1N1 influenza and those evaluated for other illnesses during the period of the pandemic.

We attribute the generally mild impact of H1N1 influenza on our patient population to several therapeutic interventions. Firstly, our patients and their families are taught to report any febrile illness or respiratory distress to the on-call hematologist and to request

evaluation in the Hematology clinic or emergency department, and these precautions were further stressed during the H1N1 pandemic. Secondly, all febrile SCD patients were immediately started on empiric antibiotic therapy and virtually all (94%) with symptoms suspicious for influenza were also started on a course of oseltamivir. Finally, patients who were admitted were maintained on oseltamivir and appropriate antibiotic coverage, and those with confirmed or suspected ACS who had hemoglobin concentrations less than 10 mg/dl received simple transfusions within 24 hr of admission (48% of all admitted patients and 85% of those with ACS or hypoxia). Although the benefit of simple transfusions in reversing early ACS has not been rigorously proven [12], our experience suggests that this practice, which is in accordance with Sickle Cell Disease Care Consortium guidelines [10], helped minimize the impact of ACS associated with H1N1 influenza infections in our patients. Of note, the previously described study of SCD patients with H1N1 influenza [8] had a lower rate of transfusion and of antiviral therapy (34% and 79% respectively), which may partially explain the better outcomes in our patient group.

Further analysis of our patient population who required admission revealed certain patient factors that correlated with disease severity. Patients with any past history of ACS were more likely to have required admission and to develop ACS than those without such a history. A history of ACS in the 12 months prior to infection with H1N1 influenza was especially significant in this regard. Additionally, a history of reactive airway disease (RAD) also correlated with increased rate of admission and of incidence of ACS, though these correlations did not achieve statistical significance. Finally, patients with a history of both ACS and RAD were especially likely to require admission and to develop ACS during H1N1 infection. While we cannot completely account for the effect of patients' prior history on the decision to admit, a review of admission documentation indicates that these decisions were generally based on clinical presentation and previously established clinical guidelines that do not include a history of past ACS or of RAD as a criterion for admission. The high rate of ACS and other clinically significant symptoms among admitted patients supports the conclusion that most admissions were for clinical illness rather than observation alone.

Chronic SCD therapy also had an effect on the severity of H1N1 illness among our patient population. None of our patients on chronic transfusion therapy for past complications developed ACS, though a significant number required hospitalization for other influenza-related symptoms. Additionally, while a significant proportion of patients on hydroxyurea therapy were admitted and developed ACS, further stratification of these patients based on HbF levels revealed that those with HbF levels above 30% were much less likely to require admission and that none of this group of patients developed ACS. Taken together, patients on chronic transfusion therapy and those on HU with HbF levels over 30% were somewhat less likely to require admission and significantly less likely to develop ACS. Furthermore, the mean hemoglobin F (HbF) levels of patients requiring admission and of those who developed ACS were significantly lower than that of patients successfully managed as outpatients and of those who did not develop ACS respectively (Table V). These results are especially striking given that patients on either of these therapies at our institution generally have had earlier and more severe complications from SCD prior to initiation of chronic therapy.

Our analysis suggests several guidelines for the management of pediatric patients with SCD during future influenza pandemics and seasonal influenza epidemics. First, SCD patients and families should be counseled to seek prompt medical attention for any febrile illnesses or respiratory symptoms. Secondly, there should be a low threshold to test patients for influenza and to initiate empiric therapy with oseltamivir. Patients with uncomplicated past history may be safely managed on an outpatient basis, but those with past complications, especially RAD or past episodes of ACS, may warrant admission for observation. SCD therapy with chronic transfusion or HU titrated to maximize HbF levels also appears to protect against ACS in the setting of influenza. Finally, early transfusion may be of benefit to treat suspected episodes of ACS. While our study did not address any of these suggestions in a prospective fashion, our results indicate that further clinical trials are warranted to establish the efficacy of these suggested guidelines.

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Abbreviations

SCD	sickle cell disease
ACS	acute chest syndrome
HU	hydroxyurea
RBC	red blood cell
RAD	reactive airway disease
CT	chronic transfusion
HbF	hemoglobin F
CCHMC	Cincinnati Children’s Hospital Medical Center

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TABLE I

Characteristics of SCD Patients Diagnosed With H1N1 Influenza

	All patients	All H1N1+ patients	Patients not admitted	Patients admitted	Patients with ACS
Age at diagnosis (years)					
Mean (SD)	—	9.3 (5.6)	8.5 (5.3)	10.3 (5.9)	9.2 (3.2)
Median	—	9.3	9.3	10.2	9.8
Gender					
Male		23	10	13 (57%)	6 (26%)
Female		25	15	10 (40%)	4 (16%)
Genotype					
SS	154	31 (20%)	14	17 (55%)	7 (23%)
SC	77	12 (15.5%)	9	4 (33%)	3 (25%)
SB+Thal	25	3 (12%)	1	2 (66%)	0 (0%)
Other	15	2 (13%)	2	0 (0%)	0 (0%)
Total	272	48 (17.6%)	25	23 (48%)	10 (21%)
SCD therapy					
Hydroxyurea		14	8	6 (43%)	4 (28.6%)
Chronic transfusion		7	3	4 (57%)	0 (0%)
None		27	14	13 (48%)	5 (18.5%)

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TABLE II

Comparison of H1N1-Positive Patients to Patients With Negative H1N1 Testing During the Pandemic

	H1N1 positive (N = 48)	H1N1 negative (N = 64)	*P*-value
Median age (years)	9.3	5.3	0.08
Proportion female	25 (52.1%)	36 (56.3%)	0.66
Genotype			
SS	31 (64.5%)	48 (75%)	0.49
SC	12 (25%)	11 (17%)	
Other	5 (10.4%)	5 (7.8%)	
HU or chronic transfusion	21 (43.8%)	14 (21.9%)	0.01
Admission	23 (47.9%)	36 (56.2%)	0.38
ACS	10 (20.8%)	14 (21.9%)	0.89
Mean duration of admission (days)	3	3.4	0.62

TABLE III

Stratification of H1N1-Positive Patients Requiring Admission by Demographics and Patient History

	Admission	*P*-value	ACS	*P*-value
Gender				
Male (N = 23)	13 (56%)	0.2524	6 (26%)	0.4869
Female (N = 25)	10 (40%)		4 (16%)	
Genotype				
SS (N = 31)	17 (55%)	0.46	7 (23%)	0.74
SC (N = 12)	4 (33%)		3 (25%)	
Other (N = 5)	2 (40%)		0 (0%)	
History of reactive airway disease				
Positive (N = 9)	7 (78%)	0.068	4 (44%)	0.075
Negative (N = 39)	16 (41%)		6 (18%)	
History of ACS				
Positive (N = 20)	14 (70%)	0.0096	7 (35%)	0.07
Negative (N = 28)	9 (32%)		3 (11%)	
ACS in past 12 months				
Positive (N = 10)	10 (100%)	0.0002	6 (60%)	0.0025
Negative (N = 38)	13 (34%)		4 (11%)	
History of pain crises				
Positive (N = 15)	9 (60%)	ND	2 (13%)	ND
Negative (N = 33)	14 (42%)		8 (21%)	
History of splenic sequestration				
Positive (N = 6)	2 (33%)	ND	0 (0%)	ND
Negative (N = 42)	21 (50%)		10 (21%)	
Seasonal influenza vaccination 2009				
Positive (N = 17)	9 (53%)	ND	4 (24%)	ND
Negative (N = 33)	14 (42%)		6 (18%)	

TABLE IV

Analysis of Patients With H1N1 Influenza on Hydroxyurea or Chronic Transfusion Therapy

	Not admitted	Admitted	*P*-value	No ACS	ACS	*P*-value
HU therapy: mean HbF level (SD)	31.2 (5.9)	14.1 (7.4)	0.0004	28.4 (8.1)	12.7 (8.5)	0.0069
Chronic transfusion: mean HbS level (SD)	25.8 (8.2)	28.4 (7.6)	0.69	27.3 (7.3)	N/A	—

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TABLE V

Stratification of Patients With H1N1 Influenza by Therapy Status

	Good response to HU or CT	Sub-therapeutic or no therapy	*P*-value
Number H1N1-positive	13	35	
Number admitted	4 (31%)	19 (54%)	0.19
Number with ACS	0 (0%)	10 (29%)	0.04