

ACUTE CHEST SYNDROME IN SICKLE CELL DISEASE IN SAUDI ARAB CHILDREN IN THE EASTERN PROVINCE

Ibrahim A. Al-Dabbous, MBBS, DCH, CABP

Background: This study was conducted to define the clinical features and outcome of acute chest syndrome (ACS) in sickle cell disease (SCD) patients in the Eastern Province of Saudi Arabia.

Patients and Methods: This was a prospective study involving patients who were 12 years or younger, admitted to Qatif Central Hospital with ACS (or developed ACS during hospitalization) between July 1992 and July 1997. Chest x-ray, CBC, cultures (blood, sputum and throat), mycoplasma titers and blood gases were performed at the onset of ACS. Oxygen therapy, antibiotics, blood transfusion and mechanical ventilation were used as required.

Results: One hundred and thirty-two patients with episodes of ACS (154 admissions which accounted for 7.7% of SCD admissions) were studied. Fever, cough and chest pain were the most common symptoms. Raised temperature, tachypnea and tachycardia were the most common findings. ACS was associated with painful crisis (46.8%) and infections (13%). It was mild in 31.2%, moderate in 57.1% and severe in 11.7% of admissions. Radiological studies revealed unilateral infiltrate in 69.5%, bilateral infiltrate in 20.8% and pleural effusion in 3.3%. There was a significant drop in Hb and platelets, and a rise in WBC. Significant hypoxia was found in 10.4% and bacteremia was found in 7.1%. Cephalosporine was required for 37%, simple blood transfusion for 74%, exchange transfusion for 2%, and mechanical ventilation for 0.7% of admissions. None of our patients died. Mean duration of hospitalization was 6.7 days.

Conclusion: Acute chest syndrome in children with sickle cell disease in the Eastern Province of Saudi Arabia is relatively mild and infrequent, and rarely associated with bacteremia

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Key Words: Acute chest syndrome, sickle cell disease, pulmonary complication.

Acute chest syndrome (ACS) is a common complication in patients with sickle cell disease (SCD),¹ causing significant morbidity and mortality.² The term "acute chest syndrome" was first suggested for this complication by Charache et al.³ in 1979, acknowledging the difficulties in determining its pathogenesis. The frequency of this complication is variable, reaching up to 45% of individuals with SCD.⁴ It accounts for more than 90% of hospital admissions.^{5,6} There is very limited information on this complication in the so-called "benign" Saudi SCD.^{7,8} This report defines the frequency, clinical and laboratory features of 154 episodes of ACS in children with SCD admitted to Qatif Central Hospital in the Eastern Province of Saudi Arabia.

Patients and Methods

All pediatric patients (12 years or younger) with SCD admitted in Qatif Central Hospital (QCH) from July 1992 to

From the Department of Pediatrics, Qatif Central Hospital, Qatif, Eastern Province, Saudi Arabia.

Address reprint requests and correspondence to Dr. Al Dabbous: P.O. Box 628, Qatif, Eastern Province, Saudi Arabia.

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July 1997 with ACS, as well as those who developed ACS during hospitalization were included. The diagnosis of SCD was confirmed by sickling test, hemoglobin electrophoresis, and family study.⁹

Acute chest syndrome is defined as an acute episode associated with clinical and/or radiological evidence of new pulmonary abnormalities in patients with SCD, and often accompanied by fever, bone pain, chest pain, cough, dyspnea, hypoxia, leukocytosis and decline in hemoglobin below the usual steady state level.^{2,10-13} Chest x-rays, complete blood counts, cultures (blood, sputum and throat) were performed on admission, or when the chest symptoms developed during the course of illness. Room air arterial blood gases were done on admission whenever possible. Mycoplasma antibody titer (complement fixation) and/or cold agglutinin titers were done if they were available. Complement fixation titer¹⁴ and cold hemagglutinin titers^{14,15} of 1:32 or more were considered significant. A simple scoring system was used to assess the degree of clinical severity: score "0" was made when there was no respiratory distress, which indicated mild disease; score "1" was made when there was tachypnea (age adjusted), which indicated moderate severity; and score "2" was made when there were tachypnea and retraction, which indicated severe

TABLE 1. Acute chest syndrome by age.

Age group	No. of patients with ACS
<2 years	5
2-4 years	35
5-6 years	30
7-8 years	34
9-10 years	28
11-12 years	22

TABLE 2. Presenting symptoms and signs of patients with ACS.

Symptoms	No.	%	Signs	No.	%
Fever	144	93.5	T<38.9°C	84	54.6
Cough	126	81.8	T>38.9°C	25	16.2
Chest pain	66	42.9	Tachypnea	106	68.8
Productive cough	50	32.5	Retractions	18	11.7
Shortness of breath	38	24.7	Tachycardia	90	58.4
Whitish sputum	35	22.7	Dullness to percussion	11	7.1
Yellowish sputum	13	8.4	Decreased breath sounds	52	33.8
Greenish sputum	2	1.3	Rales	82	53.2
			Rhonchi	5	3.3
			Bronchial breathing	9	5.8
			Normal exam	33	21.4

TABLE 3. Associated problems with ACS.

Problems	No.	%
Painful crises	72	46.8
Abdomen	25	16.2
Back	20	13
Chest	14	9.1
Extremities	13	8.4
Infections	20	13
Bacteremia	11	7.1
URTI	6	3.9
UTI	1	0.7
Acute cholecystitis	1	0.7
G6PD deficiency and acute hemolytic anemia	4	2.6
Post operative	3	2
Sequestration crisis	2	1.3
Trauma to chest	1	0.7
Bronchial asthma	1	0.7

URTI=upper respiratory tract infection; UTI=urinary tract infection.

TABLE 4. Baseline and ACS laboratory values.

Tests	Baseline (mean)	ACS (mean)	P-value
Hb (g/dL)	8.6	7.8	0.002
WBC ($\times 10^9/L$)	11.4	17.8	0.000002
Platelets ($\times 10^9/L$)	390.7	335.9	0.03
Retics (%)	7.97	8.7	0.55
S. bilirubin	3.8	3.3	0.57

disease.¹⁶ Patients with severe disease were admitted in pediatric intensive care unit.

All patients were treated with intravenous fluid. Simple analgesia (paracetamol) or narcotic analgesia was given as needed. Oxygen therapy was given for hypoxia ($PO_2 < 60$ mm Hg, or O_2 saturation $< 90\%$) and moderate-to-severe disease. Ampicillin was given to patients with mild-to-moderate disease. In patients with severe disease or patients with mild-to-moderate disease not responding to ampicillin, third-generation cephalosporin was given. Oral erythromycin was given to all patients. Vancomycin and third-generation cephalosporine were given to patients with shock, rapidly progressing disease or respiratory failure. Simple blood transfusion was given to patients with severe disease, consolidation involving one or more lobes and PaO_2 of less than 75 mmHg despite oxygen therapy. Partial

exchange blood transfusion was given to patients with rapidly progressing disease or signs of respiratory failure. Mechanical ventilation was given to those patients who deteriorate despite oxygen therapy and partial exchange transfusion.¹⁰ The information was recorded prospectively. A statistical program (Epistat package) was used to perform various statistical tests.

Results

During the study period, total admissions in pediatric medical ward in Qatif Central Hospital was 9527, of which 2010 admissions (21.1%) were for SCD complications. Of the SCD admissions, 154 (132 patients) were for ACS, which accounted for 7.7% of SCD admissions. Of the 132 patients with ACS, two patients had sickle cell beta-zero-thalassemia ($S\beta^0T$), three had sickle cell beta⁺ thalassemia ($S\beta^+T$), and 127 had sickle cell anemia (SCA).

The age of patients with ACS ranged from 9 months to 12 years, with a mean of 6.9 years. The age distribution are shown in Table 1. Of the 132 patients, 99 patients were males and 33 were females, with a male to female ratio of 3:1. Most of the patients with ACS had only one episode, but 13 patients (8.4%) had at least two episodes each. One patient with $S\beta^0T$ had five episodes of ACS and two patients with $S\beta^+T$ had two episodes each.

The presenting symptoms and physical findings at the time of hospitalization are shown in Table 2. Associated problems other than ACS are shown in Table 3. Three patients developed ACS postoperatively. One patient developed ACS three days post-splenectomy and the other two patients (one patient post-cholecystectomy and the other post-excision of dermoid cyst) developed ACS one-day post operatively.

Mild ACS was found in 48 admissions (31.2%), moderate ACS in 88 admissions (57.1%), and severe ACS in 18 admissions (11.7%).

Radiological studies showed unilateral infiltrate in 107 episodes (69.5%) and bilateral infiltrate in 32 episodes (20.8%). In the unilateral, there was more right side involvement (47.4%) than left side (20.8%). They varied by age (Figure 1). Pleural effusion was found in six episodes (3.3%). The older children had middle and lower lobe involvement significantly more often than the younger children did ($P < 0.000001$).

Laboratory findings are shown in Table 4. Hemoglobin showed a significant change during ACS, with hemoglobin dropping by an average of 1.6 g/dL. The mean of polymorphonuclear cells (PMN) was 61.5 ± 20.3 and of band cells was 5.7 ± 7.5 . Total serum bilirubin was increased in 6 (46.2%) of 13 patients with yellowish sputum, in comparison to 7 of 35 patients (20%) with white sputum, but the differences was not statistically significant ($P = 0.15$). The mean of HbF was 21.2 ± 10.3 and of MCV was 73.8 ± 10.1 .

Room air arterial blood gas sampling was performed in 26.6% (41 of 154) of admissions (Oxygen was started before arterial blood gases in the rest of admissions). Mean PaO₂ was 66.3 mm Hg, mean O₂ saturation was 88.7% and mean Pa CO₂ was 33.6 mm Hg. Thirty-nine percent (16 of 41 patients) presented with PaO₂ less than 60 mm Hg.

Bacteremia was documented in 7.1% (11 of 154) of ACS episodes. The most common organisms isolated were *Salmonella* (3 of 11) and *Streptococcus pneumoniae* (2 of 11). Other organisms isolated were *Hemophilus influenzae* (1 of 11), *Staphylococcus aureus* (1 of 11), *Staphylococcus epidermidis* (1 of 11), *Bacillus* species (1 of 11) and both *Enterobacter agglomerans* and *Acinetobacter* (1 of 11).

Urine cultures showed *Klebsiella* spp. in one patient. Sputum cultures revealed *Hemophilus influenzae*-b in one patient. Group A β-hemolytic *Streptococcus* was isolated in two patients from throat swab. Pleural fluid and other cultures showed no growth.

Serological studies for mycoplasma infections were done in 81 admissions. Positive titer was found in 35 admissions (43.2%), but significant titer was found in only 22 admissions (27.2%).

All patients received hydration and erythromycin. Ampicillin was given to 98 patients (63.6%), whereas cephalosporine was given to 57 patients (37%) and 20 (13%) were given other antibiotics. Simple blood transfusion was given to 114 patients (74%), whereas only three patients (2%) were given exchange blood transfusion. Eighteen patients required ICU care and one patient required mechanical ventilation. None of our patients died. The mean duration of hospitalization was 6.7 days.

Discussion

SCD is a major health problem in the Eastern Province of Saudi Arabia. As shown in this study, SCD-related problems accounted for more than 20% of total admissions to the pediatric medical ward. ACS is an important complication of SCD. It was listed as the cause of death in as many as 25% of patients who died of SCD.¹⁷ Accurate characterization of this complication become necessary in the Eastern Province of Saudi Arabia where SCD is relatively benign in comparison to other parts of Saudi Arabia and the world.¹⁸⁻²⁰ The frequency of 7.7% is low in comparison to other areas where the frequency may reach over 90%.⁵ It was found, as stated in other studies, that ACS was significantly more frequent in SCA than other SCD variants.^{6,11}

FIGURE 1. Age-specific radiographic finding in ACS.

Although ACS was reported more frequently in children between 2 and 4 years old,⁶ our study showed almost similar pattern in patients 2-10 years old. The frequency was slightly decreased at age 11-12 years, and very low for

those under 2 years of age. The low ACS frequency in those under 2 years was observed by others.⁶ It could have been the effect of higher Hb F concentration in those patients.

Recurrent attacks of ACS occurred in less than 10% of SCD patients in the Eastern Province, which was low in comparison to other areas^{6,11} where recurrence may occur in 20% -80%. Although ACS was associated with acute painful crises in around 50% of admissions, all patients, except three, presented with ACS at admission. This was different from other areas where ACS was diagnosed at admission in 30%-50%.^{11,21} This may suggest pulmonary infarction in our patients rather than bone marrow/fat embolism, which is quite possible in those patients who presented with severe acute painful crisis followed by ACS after admission.

The finding of yellowish sputum in 8.4% of the admissions (26% of those with productive cough) was a new feature which had not been described previously. It seemed that the yellowish sputum may be related to increase in serum bilirubin, but further studies of this association are required. It may be an important feature because yellowish sputum (probably non-infective) may be mistaken for greenish sputum, which is infective. This may play a role in the management of these patients.

Bacteremia was documented in only 7.1% of admissions. This is supported by recent reports, which showed that bacteria are an uncommon cause of ACS.¹⁻³ On the other hand, the association of acute painful crisis in around 50% of admissions may suggest that intravascular sickling in the lungs may account for much of the clinical picture in ACS. It is extremely difficult to differentiate between infarction and infection by clinical, radiological or laboratory tests.¹¹

Practically, pulmonary infarction may lead to pulmonary infection and vice versa. Therefore, infarction and infection should be considered in the management of these patients.

The finding of significant titers for mycoplasma infections in more than 40% of those who underwent serological studies for mycoplasma may support the current practice of giving erythromycin (or new macrolides) to all patients with ACS. This is also supported by recent study which showed *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were the most frequent isolated pathogens.²¹

In ACS, simple blood transfusion may be beneficial in shortening the clinical course and decreasing mortality.²²⁻²⁴ In this study, the use of simple blood transfusion in 74% of admissions may have contributed to rapid improvement of our patients.

In severe cases of ACS that required ICU, significant hypoxia and requirement of broadspectrum antibiotics were rarely found. Exchange blood transfusion and mechanical ventilation were rarely required. There was no mortality in our studied patients. These observations suggest the mild nature of ACS in the Eastern Province of Saudi Arabia,

which may also indicate the mild nature of SCD in this area.

The cause of this mild nature is not known, but genetic factors may play an important role. Perrine et al. have shown that the glycine/alanine ratio in patients from the Eastern Province (mild SCD) is significantly different from that of Jamaicans (severe SCD).¹⁸ El-Hazmi et al. have shown different β -globin gene haplotypes in Saudi Arabia depending on whether or not a specific polymorphic site of specific restriction endonuclease is present (+) or absent (-). In the Eastern Province, a haplotype (+ + - + + 5') to the β -globin gene has been identified in majority of the patients, while in the Southwestern region where the SCD is severe, a different haplotype (- - - - +) has been identified in SCA patients.^{25,26}

The mechanism by which genetic factors affect the severity of SCD is not known. Many authors have however implicated high Hb F²⁷⁻²⁹ and alpha thalassemia.³⁰⁻³³ ACS has been found to be inhibited by high Hb F levels.^{34,35} It has also been found that hydroxyurea therapy which induces high Hb F decreases the frequency of ACS significantly.^{36,37} On the other hand, α -thalassemia was not found to affect ACS frequency.⁴ In this study, we think high Hb F and probably α -thalassemia (low MCV) may have contributed to the mild nature of ACS.

In conclusion, ACS in children in the Eastern Province of Saudi Arabia is relatively infrequent, mild and rarely associated with bacteremia. This is may be part of the relatively benign nature of SCD in this area.

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