Very high levels of C-reactive protein should alert the clinician to the development of acute chest syndrome in sickle cell patients

Can Acipayam (1)
Sadik Kaya (2)
Mehmet Rami Helvaci (3)
Gül Ilhan (4)
Gönül Oktay (5)

(1) Department of Pediatric Hematology and Oncology,
Medical Faculty of Mustafa Kemal University, Hatay, Turkey.
(2) Department of Pediatric, Hatay Antakya State Hospital, Hatay, Turkey.
(3) Department of Internal Medicine,
Medical Faculty of Mustafa Kemal University, Hatay, Turkey.
(4) Department of Hematology, Hatay Antakya State Hospital, Hatay, Turkey.
(5) Hemoglobinopathy Center, Hatay Antakya State Hospital, Hatay, Turkey.

Correspondence:
Can Acipayam, MD
Department of Pediatric Hematology and Oncology
Mustafa Kemal University, Tayfur Ata Sokmen Medical School,
Serinyol, Hatay 31000, Turkey.
Phone Number: +90 326 229 10 00
Fax Number: +90 326 245 56 54
Email: cacipayam@hotmail.com

Abstract

Purpose: Acute chest syndrome (ACS) is associated with both inflammation and tissue ischemia. C-reactive protein (CRP) is a marker of systemic inflammation. The aim of this study was to determine if a relationship exists between CRP and severe ACS.

Methods: Forty-three patients with painful crises (range: 4-18 years, mean: 11.4 years) hospitalized between 2012 and 2014, consisting of 23 patients with ACS and 20 patients without ACS (uncomplicated vaso-occlusive crisis) were recruited into this study. Retrospective data were obtained directly from inpatient medical records. ACS was defined as a new pulmonary infiltrate on chest radiograph after admission and before discharge. CRP was measured using a BN II Nephelometer.

Results: Mean length of hospital stay of ACS patients was 9.9 days (range 7-18 days) while that of patients without ACS was 5.2 days (range 2-10 days), (p=0.001). In 91% of the ACS cases, ACS developed within the first 72 hours, while the remaining 9% cases were admitted for vaso-occlusive crises but subsequently developed ACS during their hospital stay on the 5th to 7th days. CRP levels on admission were significantly higher in patients with ACS than those without ACS (p=0.001).

Conclusion: We investigated CRP in relation to ACS in children with sickle cell disease (SCD). Elevated CRP was determined in all ACS patients with SCD. CRP may be a superior diagnostic marker and herald severe ACS in individuals with SCD.

Key words: Sickle cell diseases, Acute chest syndrome, C-reactive protein

Introduction

Acute chest syndrome (ACS) is a frequent complication of sickle cell disease (SCD). ACS represents grounds for hospital admission and is the most common cause of death in patients with SCD. ACS is defined as a new pulmonary infiltrate and some combination of fever, chest pain and signs and symptoms of pulmonary diseases, such as tachypnea, cough and dyspnea (1-3).

There are many causes of ACS, and the pathogenesis is complex and not thoroughly understood. The trigger for ACS in an individual patient generally cannot be identified. Although infection is the most common identifiable cause of ACS, there are other important triggers including vaso-occlusive crisis (VOC), rib infarction, bone marrow infarction, fat embolism and asthma. The presenting signs and symptoms of ACS can be highly variable and affected individuals may have a normal initial physical examination. ACS often develops in the setting of a vaso-occlusive episode or with other acute manifestations of SCD, frequently after two to three days of severe vaso-occlusive pain. ACS can progress rapidly (over several hours to days) to requiring intubation and mechanical ventilatory support (3-5).

Acute phase proteins such as C-reactive protein (CRP) are well recognized for their applications in human diagnostic medicine and are reported to be valuable in the diagnosis and prognosis of cardiovascular disease, SCD, autoimmunity, organ transplant, and cancer treatment. CRP can be used together with signs and symptoms and other tests to evaluate an individual for acute or chronic inflammatory conditions. Previous studies have reported a strong association between increased CRP levels and VOC. The elevated CRP in SCD may be in response to endothelial damage due to the blockage of the vascular endothelium by sickled erythrocytes (6,7).

As the sickle cell painful crisis is associated with both inflammation and tissue ischemia, we hypothesized that serum CRP levels may rise during and in association with severe ACS. The aim of this study was to evaluate CRP levels in children with SCD in ACS and during VOC.

Methods

We retrospectively reviewed the medical records of patients under 18 years and admitted for VOC between 2012 and 2014. Patients' data were obtained directly from inpatient medical records and from the hospital-based computer system accessed by the same physician. Data collected included demographic information such as gender and date of birth. Other variables included dates of admission and discharge. Medical charts for all patients were reviewed for data concerning the chief complaint, respiratory symptoms, fever, peripheral blood white blood cell (WBC) count, biochemical tests (blood urea nitrogen (BUN), creatinine and CRP), chest radiograph and chest computed tomography (CT) reports, receipt of blood transfusion and erythrocytapheresis, painful time, admission to hospital, duration of hospitalization, discharge diagnosis, mortality and complications during the study. The final discharge diagnosis of ACS was defined as a new pulmonary infiltrate on chest radiograph after admission and before discharge. ACS was recorded according to the current criteria: new infiltrate visible at chest X-ray (involving at least one complete lung segment consistent with the presence of alveolar consolidation) associated with one or more symptoms, such as fever, cough, tachypnea, breathing difficulties or new-onset hypoxia (8).

Blood samples were obtained during visits to the outpatient clinic or at presentation to the emergency department for a painful crisis. Standard blood counts were performed in EDTA-anti-coagulated blood (Sysmex XT- 2000i, USA). Biochemical investigation was performed with a Modular Analytics P800 analyzer (Roche Diagnostics, Indianapolis, IN) using spectrophotometric methods. We measured the inflammatory biomarker CRP in all patients using a BN II Nephelometer. Serum CRP values were considered normal between 0 and 5 mg/dl. Patients were divided into two groups, with ACS and without ACS. Patients without ACS were selected from the VOC group without complications.

Statistical Analysis

Statistical analysis was performed on SSPS for Windows version 15 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed as mean±standard deviation (SD), mean, maximum and minimum. For data analysis, patients were divided into two groups, with ACS and without. The Mann-Whitney U-test and chi-square test were used for comparison between the two groups. The chi-square test was used to evaluate qualitative variables, while the Mann-Whitney U-test was used to examine relations between non-parametric data. $p<0.05$ was considered significant.

(Results - next 2 pages)

Discussion

Serum CRP levels in patients with ACS were comparable to those in patients without, but increased significantly during the disease. ACS has a multifactorial etiology, including a variety of inciting events that trigger deoxygenation of HbS, leading to its polymerization and to red blood cell sickling with subsequent vaso-occlusion, ischemia, and endothelial dysfunction (9,10). Heightened proinflammatory cytokine production has been reported in individuals with SCA during VOC (7). Elevated levels of CRP, a general marker of inflammation, have previously been reported in ACS patients with SCD (11-14).

Previous studies from our institution have shown that serum CRP levels increase markedly in SCD patients with ACS and that sequential measurements of CRP are useful in predicting the subsequent development of ACS in patients hospitalized for VOC (11-14). This study confirms the earlier findings of increased CRP levels in patients with ACS. In contrast to other studies, CRP levels in our ACS group were significantly higher than those in

Table 1: Demographic and clinical characteristics of children with SCD admitted due to an initial painful episode over a 2-year period

Parameter	ACS n= 23	no ACS n=20	p-value**
Demographic characteristics			
Mean age (range in years)	10.4 (4–18)	12.6 (4–18)	0.63
Gender (male, %)	11 (48%)	8 (40%)	0.60
Co-morbidities (n,%)			
Asthma	0	0	1
Stroke	1(4%)	0	0.35
Hydroxyurea	6 (26%)	3 (15%)	0.37
Clinical characteristics (n,%)			
Asthma symptoms	12 (52%)	0	0.001*
Hypoxia	3 (13%)	0	0.94
Fever	23 (100%)	11 (55%)	0.001*
Cold	12 (52%)	0	0.001*
Cough	14 (61%)	0	0.001*
Simple transfusion	19 (83%)	4 (20%)	0.001*
Exchange transfusion	3 (13%)	0	0.94
Length of hospital stay (day, range)	9.9 (7-18)	5.2 (2-10)	0.001*
Duration of pain (day, range)	5.2 (3–10)	4.5 (2-7)	0.66

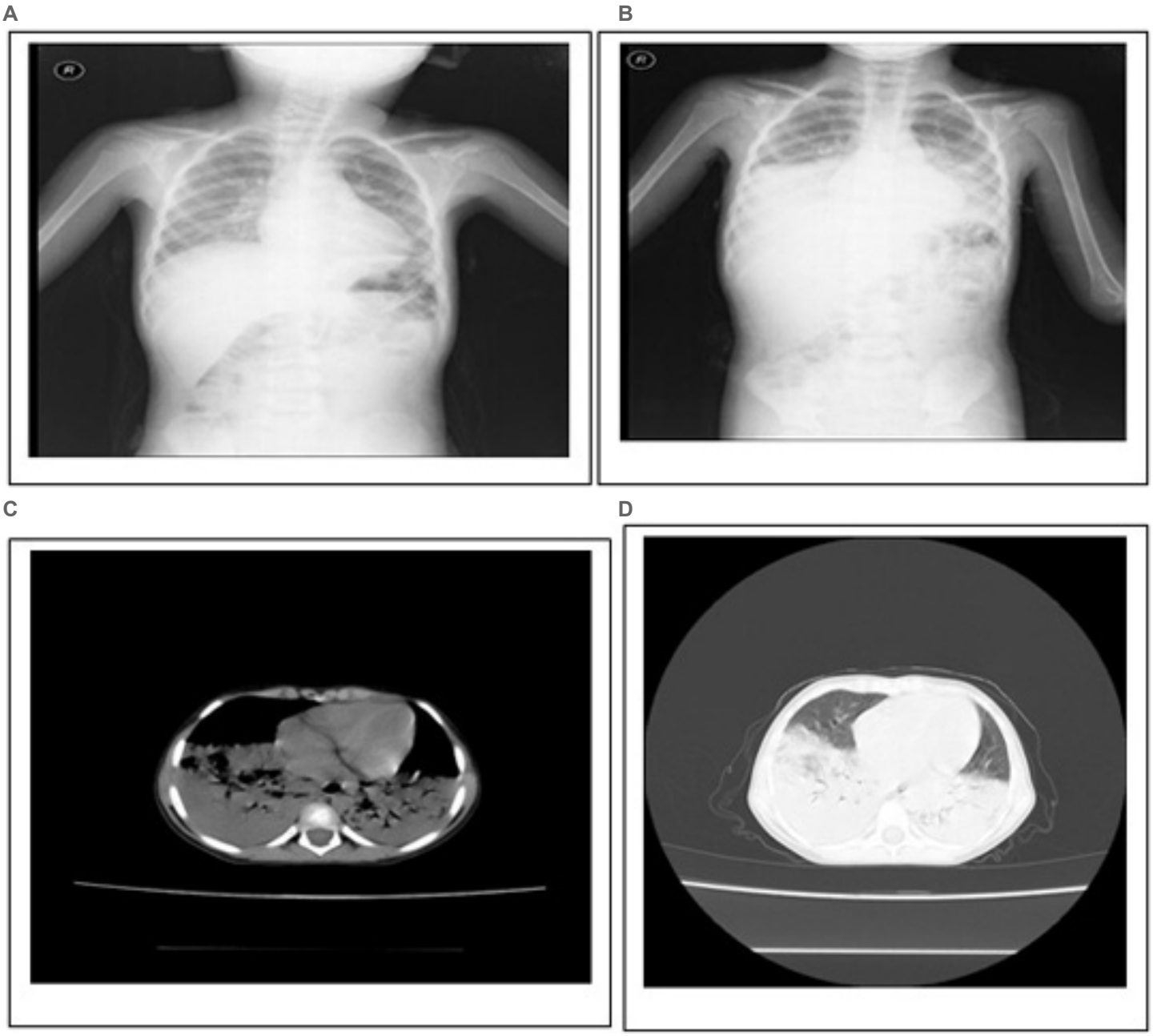
*Statistically significant at $p < 0.05$. ACS: Acute chest syndrome.
**p-values were calculated using the chi-square and Mann-Whitney U tests.

Figure 1: (page 7) >>
Chest X-ray and chest computed tomography (CT) image. At admission, chest X-ray revealed normal. (B) Within 48 hours, chest X-ray showed development of a new bilateral pulmonary infiltrate. Axial view of chest CT using mediastinal (C) and parenchymal (D) windows showed extensive bilateral pulmonary infiltrates and lobar consolidation (involvement of bilateral lung).

Table 2: Hematological and biochemical parameters of patients with or without ACS

Parameter	ACS	no ACS	p-value**
	n=23	n=20	
Hematological			
White blood cell count (/mm³)	21313±9536	16344±6344	0.93
Erythrocyte count (x 10^6 /mm³)	2.79±0.69	3.29±0.75	0.033*
Hemoglobin (gr /dl)	7.66±1.50	9.22±1.30	0.003*
Hematocrit (%)	22.05±4.08	25.95±3.31	0.004*
Platelet count (x 10^3/L)	390±168	455±195	0.47
Biochemical			
BUN (mg/dl)	8.55±2.72	8.00±2.56	0.63
Creatinine (mg/dl)	0.31±0.09	0.33±0.09	0.79
Albumin (g/dl)	4.28±0.57	4.78±0.29	0.002*
CRP (mg/dl)	94.77±52.71	43.74±50.14	0.001*

Data are arithmetical means ± SD. * Statistically significant at $p < 0.05$. ACS: Acute chest syndrome, BUN; blood urea nitrogen, CRP; C-reactive protein. **p-values were calculated using the Mann-Whitney U test.



the non-ACS group. Patients with SCD and elevated CRP levels must be closely monitored for development of ACS. Chest pain was present in 15 of the 23 patients with ACS at time of presentation and back pain in 8. One patient with chest pain developed intense abdominal pain in the right upper quadrant on the 2nd day of hospitalization. Consolidation and effusion was determined in the right lower lobe at abdominal USG and chest X-ray.

Diagnosis of ACS can be difficult at times and depends on the experience of the physician. The clinical symptoms described above should alert the physician to the possibility of ACS. Physical examination may reveal tachypnea, dyspnea, hypoxia, decreased air entry, wheezes, and rales. Physical examination alone can, at times, be unreliable in the diagnosis of ACS, and up to 60% of cases are missed by clinicians without radiological confirmation. Additionally, because pain crises often herald ACS, a chest radiograph may be indicated in patients hospitalized for pain, particularly when they develop fever and/or respiratory symptoms. It should be noted, though, that lung infiltrates may not appear in radiographs before 48 to 72 hours after onset of clinical symptoms (9). Vichinsky et al. (15) described the development of ACS within a mean 2.5 days after admission for pain. This parallels an earlier report by Bellet et al. (16) which determined abnormal chest X-ray 2.4 days after admission for pain. In agreement with previous studies, ACS developed within the first 72 hours in 21 of the 23 patients with ACS in our study. Chest X-rays were performed on all patients with clinical systems involving the respiratory system and widespread lobar consolidation was observed in all. Chest CT was performed on all patients in terms of effusion and complications. In agreement with Abbas et al.'s study (9), pulmonary infiltrates were determined on radiographs within the first 72 hours after onset of clinical symptoms in 91% of patients. Morris et al. (17) also reported the unreliability of physical examination in the detection of ACS in febrile patients with SCD: 61% of ACS cases were not clinically suspected by physicians prior to radiological diagnosis. Radiographs should therefore be taken of all patients with fever, chest pain and respiratory system symptoms for the detection of ACS.

Elevation in white cell count and decreased hemoglobin levels have been associated with developing acute pulmonary complication (4). Similarly in our study, lower hemoglobin levels were determined in patients with ACS. Although white cell count was higher in the ACS group the difference was not significant. In terms of biochemical tests, Albumin values were significantly lower in the ACS group. Hypo-albuminemia is a marker of disease severity and is associated with poor clinical outcome in acutely ill children. The decrease in plasma albumin during the acute phase response is probably due to diminished hepatic synthesis and the diversion of protein production required for host defense (14). In the largest series of its kind, Vichinsky et al. (18) evaluated 671 episodes of ACS in 538 patients to identify possible etiological factors. They reported no identifiable cause in 45.7% of cases, while infection was documented in 29.4% of cases, infarction in 16.1%, and fat embolization in 8.8% (18). We found no identifiable cause associated with ACS. All patients with ACS were hospitalized and given intravenous antibiotics, bronchodilators and analgesia. The management of ACS is primarily supportive and includes respiratory therapy, antibiotics, and, often, erythrocyte transfusion (9,19). Routine, early transfusions are indicated for patients at high risk for complications. Those who present with severe anemia, and multilobar pneumonia should receive transfusion before respiratory distress develops. In most patients with anemia, treatment with leukocyte-depleted, matched, simple transfusions is safe and effective (18). Transfusion therapy improves oxygenation within 12 to 24 hours of erythrocyte transfusion administration. In one large epidemiological study of ACS, management with transfusion was associated with a shorter length of hospitalization. Exchange transfusion is typically reserved for patients who are not sufficiently anemic to accommodate a simple transfusion or those with progressive respiratory decline or persistent hypoxia despite simple transfusion (19). In this study, exchange transfusion was performed on 3 patients due to respiratory difficulty and hypoxia findings, and a dramatic improvement was observed. Simple transfusion was performed on 19 of the 23 patients with ACS. All patients improved with intravenous antibiotics, bronchodilators, analgesia and transfusion therapies.

Conclusion

In conclusion, patients with SCD have high basal CRP and may develop ACS during VOC. Elevated CRP may herald severe ACS and be significantly related to risk factors for ACS. Additionally, CRP may be a good prognostic marker in patients with SCD and ACS. Overall, these results suggest that further studies are needed to determine whether CRP can predict the development of ACS in patients with VOC.

References

1. Bakanay SM, Dainer E, Clair B, Adekile A, Daitch L, Wells L, Holley L, Smith D, Kutlar A. Mortality in sickle cell patients on hydroxyurea therapy. Blood. 2005;105(2):545-7.
2. Golden C, Styles L, Vichinsky E. Acute chest syndrome and sickle cell disease. Curr Opin Hematol. 1998;5(2):89-92.
3. Paul RN, Castro OL, Aggarwal A, Oneal PA. Acute chest syndrome: sickle cell disease. Eur J Haematol. 2011 Sep;87(3):191-207. Morris C, Vichinsky E, Styles L. Clinician assessment for acute chest syndrome in febrile patients with sickle cell disease: is it accurate enough? Ann Emerg Med. 1999;34(1):64-9.
4. Buchanan ID, Woodward M, Reed GW. Opioid selection during sickle cell pain crisis and its impact on the development of acute chest syndrome. Pediatr Blood Cancer. 2005;45(5):716-24.
5. Akohoue SA, Shankar S, Milne GL, Morrow J, Chen KY, Ajayi WU, Buchowski MS. Energy expenditure, inflammation, and oxidative stress in steady-state

adolescents with sickle cell anemia. Pediatr Res. 2007;61(2):233-8.
6. Mohammed FA, Mahdi N, Sater MA, Al-Ola K, Almawi WY. The relation of C-reactive protein to vasoocclusive crisis in children with sickle cell disease. Blood Cells Mol Dis. 2010;45(4):293-6.
7. Akinlade KS, Atere AD, Olaniyi JA, Rahamon SK, Adewale CO. Serum copeptin and cortisol do not accurately predict sickle cell anaemia vaso-occlusive crisis as C-reactive protein. PLoS One. 2013 Nov 4;8(11): e77913.
8. Lionnet F, Hammoudi N, Stojanovic KS, Avellino V, Grateau G, Girot R, Haymann JP. Hemoglobin sickle cell disease complications: a clinical study of 179 cases. Haematologica. 2012;97(8):1136-41.
9. Abbas HA, Kahale M, Hosn MA, Inati A. A review of acute chest syndrome in pediatric sickle cell disease. Pediatr Ann. 2013;42(3):115-20.
10. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, Vera JC, Levy PS. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood. 1994;84(2):643-9.
11. Bourantas KL, Dalekos GN, Makis A, Chaidos A, Tsiara S, Mavridis A. Acute phase proteins and interleukins in steady state sickle cell disease. Eur J Haematol. 1998;61:49-54.
12. Hedo CC, Aken'ova YA, Okpala IE, Durojaiye AO, Salimonu LS. Acute phase reactants and severity of homozygous sickle cell disease. J Intern Med. 1993 ;233(6):467-70.
13. Bargoma EM, Mitsuyoshi JK, Larkin SK, Styles LA, Kuypers FA, Test ST. Serum C-reactive protein parallels secretory phospholipase A2 in sickle cell disease patients with vasoocclusive crisis or acute chest syndrome. Blood. 2005;105(8):3384-5.
14. Al-Saqladi AW, Bin-Gadeem HA, Brabin BJ. Utility of plasma transferrin receptor, ferritin and inflammatory markers in children with sickle cell disease. Paediatr Int Child Health. 2012;32(1):27-34.
15. Vichinsky EP, Haberkern CM, Neumayr L, Earles AN, Black D, Koshy M, Pegelow C, Abboud M, Ohene-Frempong K, Iyer RV. The Preoperative Transfusion in Sickle Cell Disease Study Group. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. N Engl J Med. 1995;333(4):206-13.
16. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. N Engl J Med. 1995;333(11):699-703.
17. Morris C, Vichinsky E, Styles L. Clinician assessment for acute chest syndrome in febrile patients with sickle cell disease: is it accurate enough? Ann Emerg Med. 1999;34:64-9.
18. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, Nickerson B, Orringer E, McKie V, Bellevue R, Daeschner C, Manci EA. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000;342(25):1855-65.
19. Chou ST. Transfusion therapy for sickle cell disease: a balancing act. Hematology Am Soc Hematol Educ Program. 2013;2013:439-46.