Clinical features and outcomes of hospitalized adults with sickle cell disease: A case series

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ABSTRACT

The severity of sickle cell disease may vary from asymptomatic to severe form including episodes of painful events and severe anemia. This hospital-based study was carried out to study the incidence of different clinical signs and symptoms in patients with sickle cell disease during hospitalization. Forty patients with sickle cell disease were included in the study. Hematological and clinical parameters were analyzed in each patient. Majority of the patients had episodes of painful events (65.0%), followed by fever (42.5%) and jaundice (32.5%). Fourteen patients had infection including malaria (6 patients), urinary tract infection (4 patients), septicemia (2 patients), pneumonia (1 patient), and acute calculous cholecystitis (1 patient) and 2 patients died. Patients with infection had lower hemoglobin level compared to patients without infection. Infections in these patients lead to higher morbidity and mortality rate. An early choice of antibiotics for infections along with supportive therapy for sickle cell disease can reduce the disease severity and save valuable life.

Key words: *Hospitalization, Infection, Painful event, Sickle cell disease*

Sickle cell disease is the most common inherited hemoglobin disorder worldwide. It is caused by a point mutation at 6th codon of the β-globin gene where glutamic acid is replaced by valine. Under hypoxic conditions, the red cells become rigid and sticky and appear like a crescent (sickle) shape. The severity due to sickle cell disease varies from asymptomatic to severe disease manifestation and death. Despite several advances in treatment strategies, patients with sickle cell disease are associated with multiple morbidities and early mortality. Most of the patients with sickle cell disease show the symptoms of repeated painful events and severe anemia which called for medical emergency.

The state of Odisha situated in Eastern India is a highly prevalent zone for sickle cell gene, where sickle cell disease considered as a major public health problem [1]. In a study undertaken in the tribal rich area of this state, the frequency of sickle cell gene was found to be 13.1% [2]. Despite high level of fetal hemoglobin (HbF), around 60% of these patients suffer from severe disease manifestation. The signs and symptoms of patients with sickle cell disease depend on the age of the patients, geographical area, comorbidity factors like infection, etc. Due to relative asplenic state and abnormal humoral immunity, infection was a major cause of morbidity and mortality in these patients [3,4]. There is a paucity of the literature on incidence of various clinical signs and symptoms on Indian adults with sickle cell disease, especially during hospitalization and majority of studies were focused to children with inconsistent results [5].

This study was carried out to analyze the different clinical spectrum and morbidity factors responsible for hospitalization in patients with sickle cell disease.

CASE SERIES

The cases were enrolled in the Department of Internal Medicine during January 2014–December 2014. This tertiary health-care facility caters to a population of 12 million residing at Western districts of Odisha state and Eastern part of the state of Chhattisgarh. This study was approved by the Institutional Ethical Committee and was granted ethical clearance. Written informed consent was obtained from all participants.

In a routine basis, all the patients admitted in this department during the study period were screened for sickle cell disease at sickle cell clinic of this hospital. Primary screening of suspected cases was carried out by sickling slide test and hemoglobin electrophoresis. Patients having "positive" sickling slide test and an "SS" pattern in the hemoglobin electrophoresis test were subjected to cation exchange - high-performance liquid chromatography using the VARIANT II Haemoglobin testing system; Bio-Rad Laboratories, Hercules, CA, USA, as per the manufacturer's guideline for the confirmatory test. After the final confirmation, we had recruited 40 patients with sickle cell disease for further analysis.

Along with the diagnosis of sickle cell disease, other examinations were also conducted, which includes complete

blood count, biochemical parameters (serum urea, serum creatinine, serum bilirubin-total, serum bilirubin direct, serum alanine transaminase, serum aspartate transaminase, serum glucose, and serum lactate dehydrogenase), urine, blood, and sputum examination through microscopy and culture, ultrasonography, X-ray. Since the study area is hyperendemic to malaria, all the study patients were screened for the same by immunochromatographic test.

The data were collected in an Excel sheet for further statistical analysis. The mean and standard deviation were calculated for all hematological parameters. Independent t-test was used for comparing the hematological and some physical examinations data between sickle cell disease patients with infection and without infection. GraphPad InStat Version 3.00 for Windows was used for all the statistical analysis. $p<0.05$ was considered to be statistically significant.

The mean age of the patients was 28.3±10.7 years (range: 17–57 years) with 57.5% (23/40) being male. There was no statistical difference in the age of both genders. Out of 40 patients, 19 patients were referred from peripheral hospitals. The mean hemoglobin, red blood cells, white blood cells, and platelets count were 7.49±2.47 g/dL, 3.08±1.03 ($\times10^6$/μL), 10.4±6.1 ($\times10^3$/ μL), and 191.5±120.8 ($\times10^3$/μL), respectively. During admission, the duration of hospital stay was 5.75±2.4 days. The mean and standard deviation along with range value of all the hematological, biochemical, and physical examination parameters have been illustrated in Table 1.

During admission, the patients with sickle cell disease showed different clinical signs and symptoms. Majority of patients had repeated episodes of painful events (65.0%) followed by fever (42.5%), jaundice (32.5%), severe anemia (30.0%), acute chest syndrome (12.5%), acute renal failure (10.0%) etc. Patients having severe anemia required a blood transfusion. A total of 35 units of blood had transfused which raised the mean hemoglobin level from 4.15 g/dL to 8.8 g/dL. Ultrasonography results revealed 17.5%, 10.0%, and 7.5% of patients had a large spleen, large liver, and gallstone, respectively. Similarly, X-ray results showed avascular necrosis in the femur in 2 patients (5.0%). Two patients had died. Both had episodes of painful events and infection (one patient had severe anemia with pneumonia whereas another had *Plasmodium falciparum* infection). The incidence of different clinical signs and symptoms in patients with sickle cell disease has been depicted in Table 2.

Urine or sputum or blood culture and a microscopic study showed 14 (35.0%) patients had infections. Malaria was diagnosed in 6 patients (*P. falciparum* in 4 patients, *Plasmodium vivax* in one patient, and both *P. falciparum* and *vivax* in one patient). Urinary tract infection was found in four patients. Pneumonia and acute calculous cholecystitis were reported in one patient each. Two patients had septicemia and both the patients were characterized by the presence of *Escherichia coli* found in blood culture.

Patients with infection had significantly low hemoglobin level and red blood cells counts whereas parameters such as white blood cells, lactate dehydrogenase, heart rate, body temperature, and duration of hospital stay were increased in patients with infection (Table 3). Out of 26 patients with an episode of painful events, 7 (26.9%) patients had infections.

Patients were discharged after appropriate treatment. Out of the 40 patients, 22 patients were under hydroxyurea therapy at a low and fixed dose of 10 mg/kg body weight/day before admission to the hospital. From the 22 patients, 10 patients had an infection and 7 patients had episodes of painful events. Acute chest syndrome, chronic kidney disease, viral fever, jaundice, and acute renal failure were reported in one patient each. Rest patients

Table 1: Demographic, hematological, and clinical examination of the study patients (n=40)

Parameters	Mean±SD	Range
Mean age	28.3±10.7	18–57
Gender		
Male	23 (57.5%)	
Female	17 (42.5%)	
Hemoglobin (g/dL)	7.49±2.47	2.1–11.3
Red blood cells ($\times10^6$/μL)	3.08±1.03	0.71–6.2
White blood cells ($\times10^3$/μL)	10.4±6.1	2.8–28.1
Platelets counts ($\times10^3$/μL)	191.5±120.8	73–731
Glucose (U/L)	105.8±24.4	57–157
Serum urea (mg/dL)	43.2±32.5	10–143
Serum creatinine (mg/dL)	1.3±0.9	0.2–4.1
Serum bilirubin-total (mg/dL)	3.0±1.5	1.1–8.0
Serum bilirubin-direct (mg/dL)	1.02±0.6	0.3–2.8
Serum ALT (U/L)	56.8±45.2	16.8–216
Serum AST (U/L)	65.5±45.4	16.9–238
Serum lactate dehydrogenase (U/L)	706.2±488.1	213–2004
Diastolic blood pressure (number)	71.0±9.0	56–98
Systolic blood pressure (Number)	108.9±12.9	82–140
Heart rate (Number)	98.3±11.8	78–119
Temperature (°F)	99.7±2.3	98–104
Hospital stay (in days)	5.75±2.4	3–12

SD: Standard deviation, ALT: Alanine transaminase, AST: Aspartate transaminase

Table 2: The incidence of clinical signs and symptoms in the study population (n=40)

Clinical signs and symptoms	Number (%)
Fever	17 (42.5)
Severe anemia	12 (30.0)
Painful events	26 (65.0)
Hepatomegaly	4 (10.0)
Cholelithiasis	3 (7.5)
Splenomegaly	7 (17.5)
Avascular necrosis	2 (5.0)
Jaundice	13 (32.5)
Acute chest syndrome	5 (12.5)
Acute renal failure	4 (10.0)
Chronic kidney disease	1 (2.5)
Death	2 (5.0)

Table 3: Comparison of hematological and physical examination parameters between sickle cell disease patients with and without infection

Parameters	With infection (n=14)	Without infection (n=26)	Independent test p value
Hemoglobin (g/dL)	6.0±2.3	8.3±2.2	0.0032*
Red blood cells ($\times 10^6/\mu L$)	2.58±0.95	3.35±1.0	0.022*
White blood cells ($\times 10^3/\mu L$)	15.4±6.5	5.3±1.5	<0.0001*
Platelets counts ($\times 10^3/\mu L$)	229.5±164.3	170.4±86.2	0.14
Glucose (U/L)	106.2±22.7	106.7±22.8	0.94
Serum urea (mg/dL)	46.7±23.2	44.5±36.9	0.73
Serum creatinine (mg/dL)	1.4±0.75	1.2±1.0	0.53
Serum bilirubin-total (mg/dL)	3.3±1.6	2.8±1.4	0.36
Serum bilirubin-direct (mg/dL)	1.1±0.7	1.0±0.54	0.57
ALT (U/L)	43.5±22.0	58.9±49.4	0.25
AST (U/L)	51.3±18.8	66.5±42.4	0.21
Lactate dehydrogenase (U/L)	936.9±552.7	581.9±408.8	0.026*
Diastolic blood pressure (mm-Hg)	68.2±8.3	72.5±9.2	0.088
Systolic blood pressure (mm-Hg)	104.1±12.9	111.4±12.4	0.158
Heart rate (beats per minute)	107.6±6.4	93.3±10.9	<0.0001*
Temperature (°F)	102.3±1.7	98.3±0.9	<0.0001*
Duration of hospital stay (in days)	7.6±2.2	4.7±1.4	<0.0001*

***p<0.05 (statistical significance). ALT: Alanine transaminase, AST: Aspartate transaminase**

were enrolled for hydroxyurea therapy at a low dose as per the guidelines. The febrile patients were started with antibiotics Antibiotic treatment was modified as per the microbiological report and continued till patients' afebrileness.

DISCUSSION

Sickle cell disease is a major public health problem in the Western districts of Odisha state with significant morbidity and mortality. The study population presented with varied clinical signs and symptoms. The majority had episodes of painful events (65.0%) and severe anemia required blood transfusion (30.0%). In a recent study undertaken in Riyadh, the authors have reported 84.0% and 28.3% of cases had episodes of painful events and anemia, respectively [6]. These varied clinical presentations can be explained by the different sickle haplotypes as evidenced by the differences in the clinical characteristics [7-9]. The β^S allele in the Indian patients is linked to Arab-Indian haplotypes which are characterized by the presence of a high HbF level with reduced clinical severity [10]. During hospitalization, these patients showed a high level of hemolysis which can be explained by low hemoglobin level with a high level of lactate dehydrogenase and bilirubin level. Raised lactate dehydrogenase level was found to be associated with increased episodes of painful events in patients with sickle cell disease [11,12]. In our study, patients with episodes of painful events also have significantly high lactate dehydrogenase level as compared to patients without painful events (median, 819 U/L versus 517 U/L).

Infection was a major cause of morbidity and mortality in patients with sickle cell disease that required hospitalization [4,13]. Out of the 14 patients with infection, majority have urinary tract infection followed by malaria. The study area is hyperendemic to malaria and contributes to significant morbidity and mortality in patients with sickle cell disease. In a recent hospital-based study undertaken in our institution, the mortality rate was significantly high (χ^2=10.48; p<0.001) in malaria patients with sickle cell disease compared to normal β-globin genotype [14]. Bacterial infection was reported in nine patients in this study. In an earlier study carried out in patients with sickle cell disease in this institution different strains of bacterial infections have also been recorded [15]. Patients with infection had low hemoglobin level with high lactate dehydrogenase level implying a higher rate of hemolysis in these patients compared to those without infection. Infection was the precipitating factor for painful events in 26.9% of patients. Patients with fever were started antibiotics, and the antibiotics were modified according to the microbiological reports.

Hydroxyurea therapy has been used significantly for the reduction in the rate of painful events and recruitment of blood transfusion and other severity in patients with sickle cell disease. Surprisingly, 55.0% (22/40) of patients were found under hydroxyurea therapy before admission to the hospital. Except for infections and chronic kidney disease, 10 patients were found irregular on hydroxyurea treatment follow-up. Death was recorded in two patients. Pneumonia and *P. falciparum* malaria was the cause of death. Death due to *P. falciparum* malaria in patients with sickle cell disease has been reported from this institution in an earlier study [14].

CONCLUSION

Painful events and severe anemia were two major clinical severities responsible for the hospitalization of patients with sickle cell disease. Infection such as bacterial and malaria accelerate the severity leading to higher morbidity and mortality in patients with sickle cell disease. It is important for the early choice of

appropriate antibiotics and other chemoprophylaxis to combat the disease severity due to infection in patients with sickle cell disease.

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