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RESEARCH ARTICLE

Factors responsible for mortality in patients with sickle cell disease: A hospital-based study

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ABSTRACT

Background: Sickle cell disease is the most common hemoglobin disorders in the state of Odisha with a significant morbidity and mortality. Various factors are responsible for the mortality in patients with sickle cell disease. **Aims and Objectives:** This study was undertaken to explicate the possible cause of mortality in patients with sickle cell disease hospitalized in a tertiary health-care facility. **Materials and Methods:** From June 2017 to December 2018, 22 hospitalized sickle cell disease patients had died. All the demographic, hematological, and clinical investigations of the deceased patients were compared with age- and gender-matched hospitalized sickle cell disease patients who survived and were discharged during this study period. All the demographic features, hematological, and clinical investigations were compared in both the deceased and survived patients. The Statistical Package for the Social Sciences version 16.0 software was used for all possible statistical analyses and $P < 0.05$ was considered as statistically significant. **Results:** Majority of the deceased patients were belonging to rural area (90.19%) which was significantly high ($P = 0.0271$) compared to survived patients (61.36%). Further, 77.27% of deceased patients were referred from primary health centers compared to 29.55% of patients in survived group ($P = 0.0007$). All the hematological and clinical parameters were comparable in both the groups. **Conclusion:** There was a high risk of mortality in patients with sickle cell disease who either referred from other primary health centers and/or belonging to the rural area. An early diagnosis of sickle cell disease, choose of suitable antibiotics, and other therapeutic strategies in hospitalized sickle cell disease patients may combat the disease severity as well as mortality.

KEY WORDS: Sickle Cell Disease; Mortality; Painful Event; Southern Odisha

INTRODUCTION

Sickle cell disease is the most common inherited hemoglobin disorder caused by a point mutation that occurs at 6th codon of the β-globin gene, in which amino acid glutamic acid is replaced by valine (GAG→GTG). Sickle cell disease accounts for a significant morbidity and mortality worldwide. In sickle cell disease, the red blood cells become rigid and sticky and are looked like a crescent (sickle) shape under deoxygenation condition. The clinical severity of patients with sickle cell disease is diverged and ranging from steady state to severe disease manifestation and death. With many control and management strategies for sickle cell disease, India ranks second worst affected country for sickle cell disorders worldwide.[1]

Majorities of the patients with sickle cell diseases usually presented with painful events ranging from a milder to severe

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form or requirement for blood transfusion which necessitate for hospitalization. Due to lack of awareness, accurate diagnosis of diseases, and proper management systems, patients with sickle cell diseases usually die. In a hospital-based study undertaken in adults from Western Odisha, the mortality rate was found to be 5%.[2] The various factors responsible for death in patients with sickle cell disease are the relative asplenic state, abnormal humoral immunity and infections, etc.[3-5] There is a paucity of literature on the risk factors associated with mortality in sickle cell disease in India. This observational study was carried out to elucidate the possible cause of mortality in patients with sickle cell disease admitted in a tertiary health-care facility.

MATERIALS AND METHODS

This study was carried out in the Department of Physiology, Maharaja Krishna Chandra Gajapati Medical College, Berhampur, Odisha (19.3076°N and 84.8110°E). This tertiary health-care facility caters to a population residing at Southern districts of Odisha state and Northern part of the state of Andhra Pradesh. In the state of Odisha, the prevalence of sickle cell gene is found to be 13.1%.[6] The incidence of sickle cell in the study area has also been reported from earlier study.[7]

Study Subjects

Sickle cell disease patients who died during hospitalization from June 2017 to December 2018 in this hospital were considered in this study. For comparison of required data, age- and gender-matched 44 sickle cell disease patients who were hospitalized during this same study period and were discharged from this hospital after clinical recovery were considered.

Laboratory Investigations

In a routine diagnosis basis, suspected patients admitted in the department of pediatrics and department of medicine were advised for diagnosis of sickle cell disease at the department of pathology. The primary screening for sickle cell disease was done by sickling slide test. If the blood sample found positive in the slide test, the sample was subjected to cation-exchange high-performance liquid chromatography using the VARIANT II hemoglobin testing system (Bio-Rad Laboratories, Hercules, CA, USA). The diagnosis of sickle cell disease was made as per the manufacturer's guideline of the instrument. Along with the diagnosis of sickle cell disease, complete blood counts and other biochemical parameters have been analyzed.

Data Collection

All the demographic, hematological, and clinical data associated with the cases were collected in a predesigned case format from the information sheet of the patients during hospitalization.

Statistical Analysis

All the data were entered into a Microsoft Office Excel file for statistical analysis. The demographic and hematological parameters data were presented as median and interquartile range or number and percentage of patients with given features. Categorical data were analyzed using Chi-square test. Independent *t*-test was used for comparing the hematological and some physical examination data between deceased sickle cell disease patients with survived sickle cell disease patients. The Statistical Package for the Social Sciences version 16.0 software was used for all the statistical analyses. $P < 0.05$ was considered to be statistically significant.

The present study was approved by the Institutional Ethical Committee of M.K.C.G. Medical College, Berhampur, Odisha, India.

RESULTS

A total of 22 patients were died who were diagnosed with sickle cell diseases during hospitalization in this tertiary health-care center during the study period. Forty-four patients with sickle cell disease, who were age and gender matched with deceased patients were enrolled in this study. The median age of the patients was 20.5 years (range, 13–50 years old). In each group of patients, 77.3% of cases were male and 22.7% of cases were female. More than 90% of deceased patients were belonging to rural area which is found to be significantly high ($P = 0.0271$) from the survived patients in which 61.36% of cases belonging to the rural area. Patients in both the groups were admitted in this tertiary care center either directly or referred from other primary health-care services. In the deceased patient group, 22.73% of cases were attained directly to this tertiary health-care facilities compared to 70.45% of cases in survived patient group ($P = 0.0007$). The demographic features are illustrated in Table 1.

The physical examinations of the patients in both the groups revealed no significant differences in systolic pressure and diastolic pressure, but the heart rate was found to be significantly high in deceased patients ($P = 0.003$). The proportion of cases with fever and/or painful events was found to be higher in deceased patients group compared to the survived patient group. Other clinical observations such as severe anemia, splenomegaly, hepatomegaly, and jaundice were comparable in both the groups. Ultrasonography has been carried out in 12 deceased patients while in all the 44 survived patients. The clinical observation in both the group of patients is shown in Table 2.

From 22 deceased patients, 2 patients died before their hematological investigations could be completed. The median fetal hemoglobin and sickle hemoglobin level in deceased patients were found to be 15.5% (range 4.8–26.1%) and 79.0% (range 69.5–89.8%). In survived patients, the median

Table 1: Demographic features of the hospitalized sickle cell disease patients (*n*=66)

Parameters	Patients (died) (*n*=22)	Patients (survived) (*n*=44)	*P* value
Age, median (IQR*)	20.5 (17–29)	20.5 (17–29)	0.999
Gender			
Male, *n* (%)	17 (77.27)	34 (77.27)	0.999
Female, *n* (%)	5 (22.73)	10 (22.73)	
Patients belonging to			
Urban, *n* (%)	2 (9.09)	17 (38.64)	0.0271
Rural, *n* (%)	20 (90.91)	27 (61.36)	
Admitted to the hospital			
Directly, *n* (%)	5 (22.73)	31 (70.45)	0.0007
Referred, *n* (%)	17 (77.27)	13 (29.55)	

IQR: Interquartile range

Table 2: Clinical observation of the hospitalized sickle cell disease patients

Clinical examination	Patients (died)		Patients (survived)		*P* value
	Cases analyzed	Incidence number (%)	Cases analyzed	Incidence number (%)	
Fever	21	16 (76.19)	44	19 (43.18)	0.0257
Painful events	22	19 (86.36)	44	23 (52.27)	0.0146
Anemia	21	11 (52.38)	44	27 (61.36)	0.6758
Splenomegaly	12	8 (66.67)	44	20 (45.45)	0.3286
Hepatomegaly	12	9 (75.0)	44	17 (38.64))	0.0558
Jaundice	16	12 (68.75)	44	18 (40.90)	0.1060

fetal hemoglobin and sickle hemoglobin level were found to be 16.8% (range 7.3–38.4%) and 75.5% (range 53.3–88.9%). There was no statistically significant difference in hemoglobin F and hemoglobin S level between the deceased and survived patients. All the complete blood count parameters including hemoglobin, red blood cells, white blood cells, mean corpuscular volume, and platelet counts were comparable in both the patient groups. The comparisons of hemoglobin variants value and complete blood counts are shown in Table 3.

DISCUSSION

In this study, the demographic, clinical, and hematological parameters were compared between 22 deceased sickle cell disease patients with 44 age- and gender-matched hospitalized sickle cell disease patients. The median age of the patients was 20.5 years. However, the oldest patient recruited in this study was 50 years old. The male patients (77.27%) were higher compared to females. In the comparison of clinical features between the groups, incidence of fever was high (76.19%) in deceased patients. The episodes of painful events were observed in 86.36% of deceased patients compared to 52.27% of survived patients. Majority (90.91%) of deceased patients belonging to the rural area and also referred from other primary health-care services (77.27%), and both the occurrences were significantly higher from the survived patients.

The age of the deceased patients indicated an early mortality in patients with sickle cell disease. Our data were found to be in accordance with the study of Ogun *et al*. (2014)[8] undertaken in Nigerian sickle cell disease patients with a median age of mortality of 21 years but were lower compared to 42 years of median age reported by Platt *et al*. (1994).[9] The increased survivability in patients with sickle cell disease may be due to the advanced prophylaxis and management strategies. The male-to-female ratio is approximately 3:1. This predominance of male patients in this study may be due to the higher level of physical activity and exertion.[10] Majorities of the deceased patients had presented with fever and significantly higher in number compared to survived patients. Although the main cause of fever has not been analyzed, the possibilities of both bacterial and protozoan infection, especially *Plasmodium falciparum,* cannot be ignored. Recently, a study from the state of Odisha (Western Odisha), infection was found to be responsible for the higher morbidity and mortality in hospitalized sickle cell disease patients in tertiary health-care facilities.[2] The occurrence of malaria in sickle cell disease patients increased the morbidity and mortality rate.[11] In a study from malaria endemic region, the mortality rate was found to be significantly increased (Chi-square, 10.48; $P = 0.001$) in sickle cell disease patient infected with severe *falciparum* malaria compare to normal red cells with severe *falciparum* malaria.[12]

Table 3: Comparison of hematological and physical examination parameters between hospitalized deceased sickle cell disease patients and survived sickle cell disease patients

Parameters	Patients (died) (*n*=22) median (IQR)	Patients (survived) (*n*=44) median (IQR)	*P* value
Hemoglobin (g/dL)	6 (5.1–8.6)	6.9 (5.1–8.3)	0.692
Red blood cells ($\times 10^6/\mu L$)	2.88 (1.19–5.42)	2.68 (1.78–3.64)	0.926
White blood cells ($\times 10^3/\mu L$)	14.17 (9.44–19.86)	12.32 (9.19–18.69)	0.485
Mean corpuscular volume (fL)	79.9 (69.95–87.9)	79.5 (69.45–89.2)	0.918
Platelets counts ($\times 10^3/\mu L$)	206 (123–266.5)	143.6 (158–309)	0.528
Diastolic blood pressure (number)	62 (60–71)	70 (66–77)	0.089
Systolic blood pressure (number)	96 (89–115)	110 (94–116)	0.088
Heart rate (number)	114 (92–118.5)	98 (87.5–107)	0.003

IQR: Interquartile range

Most of the studies undertaken in hospitalized patients, painful events remain the main cause responsible for hospitalization or mortality.[10] In this study, high occurrence of fever and painful events in deceased patients supported the observation that infection as a precipitating factor for painful events in sickle cell disease patients. A study from the Western Odisha reported that around 30% of hospitalized sickle cell disease patients having painful events had infection.[2] Higher fetal hemoglobin level reported to be associated with reduced rate of painful events in sickle cell disease patients.[13] However, in spite of the high fetal hemoglobin level in our patients, they usually suffered with significant clinical severity with repeated painful events, leading to hospitalization. This may be due to other associated factors like infections as 76.19% of deceased patients had presented with fever in this study. The fetal hemoglobin level was found to be lower in deceased patients (median, 15.5%) compared to survived patients (median, 16.8%), though it did not reach any statistical significance.

Both high incidence of referred cases and increased number of patients belonging to the rural area in deceased groups clearly remark the lack of advanced facilities for diagnosis and management of sickle cell disease in rural area for which the sickle cell disease patients with severity referred to tertiary health-care facilities. The diagnosis of sickle cell disease usually investigated when the patients present with severe complications during hospitalization.[14] This needs for an early better diagnosis, management facilities, and necessary awareness in both public and treating physicians to combat the morbidity and mortality due to sickle cell disease.

CONCLUSION

The painful events and fever are the triggering factors for the mortality in hospitalized sickle cell disease patients. The number of deceased patients who were referred from primary health center was significantly more compared to patients who directly attain the tertiary health-care facilities. Similarly, the number of deceased patients who were belonging to the rural area was significantly more compared to patients who belong to urban areas. It is essential for early diagnosis of the sickle cell disease, early option of suitable antibiotics when necessary, and other management strategies for early recovery of hospitalized patients with sickle cell disease.

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