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Sickle cell disorder: A clinical and hematological outline of pediatric patients at a tertiary care teaching hospital in eastern India

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Abstract
Sickle cell anemia resulting from homozygosity for hemoglobin S ($\beta^s\beta^s$) is a serious condition while heterozygosity for hemoglobin S ($\beta\beta^s$), referred to as sickle cell trait, is usually asymptomatic. Sickle cell hemoglobinopathy is the best known hereditary blood disorder frequently seen in rural tribal population of eastern India with a prevalence as high as 30%. It is a genetically transmitted hemoglobinopathy responsible for considerable morbidity and mortality. This study was therefore undertaken to evaluate the clinical profile and correlate it with the hematological parameters of patients with sickle cell disease in a tertiary care hospital. This is a prospective observational study analysed from January 2018 to May 2019. All patients diagnosed as sickle cell disease and sickle cell trait were taken in this study. Other hemoglobinopathies associated with Hemoglobin S were not taken for analysis. A total of 61 patients in a period of approximately one and half year were evaluated, of which forty seven had sickle cell disease and 14 had sickle cell trait. Morbidity events were commonly observed in 5-12 years of age groups (68.85%). Seasonal variation was also observed, 47.54% of total cases were seen in winter season. Pain (60.65%) was the most common presenting symptom. Severe pallor (39.34%) and splenomegaly (24.59%) was the most common sign in both groups. Vaso-occlusive crisis (59.01%) was the most common morbidity event observed, of which abdominal pain was the most common site of pain. On statistical analysis, there was significant difference seen in illness and characteristics in both the groups. In patients with sickle cell disease acute painful crisis (59.57%) attributed to vaso-occlusion was very frequent even without the presence of precipitating factors while in sickle cell trait patients, acute painful episodes was associated with acute febrile illness (71.42%).

Keywords: Sickle cell anemia, sickle cell trait, morbidity, mortality, hematological parameters

Introduction
Sickle hemoglobin was the first hemoglobin variant discovered and its characterization was well described at the biochemical and molecular level [1]. Sickle-cell anemia, results from inheritance of Hemoglobin S which results from a point mutation whereby hydrophilic glutamic acid is replaced by hydrophobic valine at the 6th codon of the β-globin gene. This substitution is due to a single nucleotide mutation (GAG/GTG) and when inherited in an autosomal codominant fashion causes devastating effects in deoxygenated state. The erythrocytes change from the normal discoid shape to sickle shape and furthermore the fragility of red cell membrane increases [1].

The hallmark of sickle cell pathophysiology is the intraerythrocytic polymerization of Deoxyhemoglobin S which results as a result of deoxygenation and determines the rheologic impairment of sickle erythrocytes as well as the change in morphology. Thus, the intracellular concentration of HbS, and fractional content of other hemoglobin variants and the percent oxygen saturation affect the polymerization rate which correlate with the rate of hemolysis and vaso-occlusion in sickle cell syndromes i.e. all conditions with E6V mutation including sickle cell trait [2]. Considering our huge population size, more than 50% of the world's sickle cell anemia syndromes are in India. It is estimated that most of these cases are reported in Central and South India [3]. In individuals with sickle cell anemia (SS), the HbS level is more than 90% while in sickle cell trait, the HbS level is less than 50% and hence the clinical manifestations of disease are usually absent or mild among sickle cell trait patients as compared to sickle cell disease [4].

The term Sickle cell diseases includes only those genotypes associated with varying degrees of chronic hemolytic anemia and vaso-occlusive pain like- sickle cell anemia (HbSS), sickle-HbC disease, sickle-β^0 thalassemia ($HbS\beta^0$) and sickle- β^+thalassemia ($HbS\beta^+$). It doesnot include sickle cell trait. One of the first manifestations of sickle cell disease, is acute dactylitis which occurs between 6-12 months and majority before the age of 6 years. It is the consequence of bone marrow necrosis of the hands and feet due to vaso-occlusion of the small vessels. Acute chest syndrome, pulmonary fibrosis, pulmonary hypertension, cerebral infarction, cardiomegaly, heart failure, hyposthenuria, proteinuria, splenic infarction, sickle retinopathy, leg ulceration are some of the commonly encountered complications of this disease. Although HbSS is the most severe form of the disease, with shortest life expectancy (median age, 42 years for men and 48 years for women), there is a tremendous heterogeneity even within this group. Sickle cell trait is nearly 40 times more than sickle cell anemia and is rarely associated with severe clinical or hematological manifestations though they may be at higher risk of hematuria, renal papillary necrosis, risk of splenic infarction at high altitude, chronic kidney disease and venous thromboembolism in comparison to the normal population [4, 5].

In India, sickle cell disease is a common hemoglobinopathy, next only to thalassemia. Sickle cell anemia was first described in south Indian tribal groups and subsequently in central India [6]. The clinical manifestations of sickle cell anemia (SCA) begin early in life after the fetal hemoglobin starts decreasing and the concentration of hemoglobin S increases within the erythrocytes [7]. Hence, the Vaso-occlusive painful episodes become more frequent as one ages [8]. This study was conducted to analyze the clinical symptoms and hematological profile of pediatric patients with sickle cell disorder.

Material and Methods

This study was conducted at a tertiary care teaching hospital IMS and Sum hospital, Bhubaneswar, Odisha for a period of one and half years. This was a prospective observational study. The study period was from January 2018 to May 2019. Patients with Sickle cell disease or trait, who were hospitalized for any morbidity in pediatric ward were enrolled for the study. The study was approved by the Institutional Ethics Committee and a written informed consent was obtained from parents of all study participants. A detailed history and clinical examination of the enrolled patient was done as per the pre-structured proforma. Baseline hematological investigations were done at the time of admission. Complete demographic, socioeconomic, clinical and hematological profile was taken. The degree of malnutrition was assessed by BMI (body mass index).

The inclusion criteria was all the diagnosed cases of sickle cell disease and trait admitted in ward with any morbidity events in the age 6 months to less than 14 years in both gender.

The exclusion criteria were patients more than 14 years age. Sickle cell disease with associated genetic or metabolic disease and sickle-beta-thalassemia patients were not included in this study.

The data was entered in an MS Excel spreadsheet and imported into Epi-Info software for statistical analysis. Result analysis was done by calculating frequencies and proportions for qualitative variables and mean were calculated for quantitative variables.

Result

Total 61 sickle cell disease patients were admitted over a period of one year and five months. Out of which 47 were homozygous sickle cell disease and 14 heterozygous sickle cell trait patients. Of the 61 patients, 39(63.93%) were male and 22(36.06%) were female. Male to female ratio was 1.7:1.

Seasonal variation played a role in precipitating the vaso-occlusive episodes and patient admission. 29(47.54%) patients were admitted in winter season (November-February), while fewer cases presented in summer (27.86%) and monsoon season (24.59%) each (Table. 1).

Table 1: Month wise distribution of sickle cell disease and trait patients.

Month	Sickle cell disease (N=47)	Sickle cell trait (N=14)	Total (N=61)
Nov-Feb	23 (48.93%)	6 (42.85%)	29 (47.54%)
Mar-Jun	12 (25.53%	5(35.71%)	17 (27.86%)
Jul-Oct	12 (25.53%)	3 (21.42%)	15 (24.59%)

Table 2 shows that in both the groups pain (60.65%) was the commonest symptom, seen in more than half of the patients. In sickle cell disease patient pain (65.95%) was the most common symptom followed by fever (36.17%) and cough (17.02%). Pallor (46.80%) and splenomegaly (27.65%) was the common sign observed. Four sickle cell disease patients had massive splenomegaly attributed to splenic sequestration. In sickle cell trait patients pain was presenting symptom in 42.85% of cases, fever in 28.57% and cough in 28.57% of cases. Severe anemia was seen in 14.28% and splenomegaly in 14.28% of cases.

Table 2: Clinical profile of patients with sickle cell disease and trait

Sign and symptoms	Sickle cell disease (N=47)	Sickle cell trait(N=14)	Total (N=61)
Pain	31 (65.95%)	6(42.85%)	37 (60.65%)
Fever	17 (36.17%)	4 (28.57%)	21 (34.42%)
Cough	8 (17.02%)	4 (28.57%)	12 (19.67%)
Vomiting, Diarrhea	2(4.25%)	3 (21.42%)	5(8.19%)
Pallor	22 (46.80%)	2 (14.28%)	24 (39.34%)
Icterus	5 (10.63%)	1(7.14%)	6 (9.83%)
Hepatomegaly	3(6.38%)	1 (7.14%)	4 (6.55%)
Splenomegaly	13(27.65%)	2 (14.28%)	15 (24.59%)

Table 3 lists the hematological parameters of the sickle cell trait and sickle cell disease patients. Sickle cell disease patients had a higher leukocyte count during Vaso-occlusive crises which is statistically significant. Platelet count was low in sickle cell disease as compare to sickle cell trait but statistically not significant. The low platelet count can be attributed to the splenic sequestration crises observed in patients of sickle cell disease.

Table 3: Hematological profile of sickle cell disease and trait patients on admission.

Investigation	Disease (N=47)	Trait (N=14)	P value
Hemoglobin (gm/dl)	8.08±2.40	10.07±2.47	<0.001
Hematocrit (%)	23.34±6.40	31.2±2.75	<0.05
MCV (micro liters)	75.99±2.12	82.6±3.01	<0.001
MCH (Picograms)	25.02±1.11	25.8±1.19	<0.05
MCHC (gram/dl)	26.03±1.86	25.57±1.28	0.109
Total leucocyte count (cumm)	14158±7859	6841±2923	<0.001
Platelet (lac/cumm)	2.75±1.30	3.07±0.86	0.154

Acute painful crisis (45.9%) and severe anemia (39.34%) were the common morbidity events in both groups. Vaso-occlusive crisis was seen in 55.31% sickle cell disease patient and 14.28% sickle cell trait patients when precipitated by a stress. Aplastic crisis was seen in 14.28% of sickle cell trait patient. Respiratory infections were seen in 28.57% and malaria in 7.14% of patients with sickle cell trait. Acute chest syndrome was seen in 2.12% of patient with sickle cell disease. Severe anemia was seen in 46.80% of sickle cell disease and 14.28% of sickle trait patients. Cardiovascular complications, stroke and dactylitis were not seen (Table. 4).

Table 4: Morbidity events in patients with sickle cell disease and trait.

Morbidity events		Sickle cell disease (N=47)	Sickle cell trait (N=14)	Total (N=61)
Acute Painful crisis	Vaso-occlusive crisis	26 (55.31%)	2(14.28%)	28(45.9%)
	Aplastic crisis	2 (4.25%)	2(14.28%)	
Acute febrile illness	Respiratory infection	5 (10.63%)	4(28.57%)	22(36.06)
	Viral fever	6 (12.76%)	3(21.42%)	
	Malaria	0	1 (7.14%)	
	Acute gastroenteritis	1 (2.12%)	2(14.28%)	
Acute chest syndrome		1 (2.12%)	0	(1.63%)
Severe anemia (h b<7gm/dl)		22 (46.80%)	2(14.28%)	24(39.34%)

Discussion

In this study 47 diagnosed cases of homozygous sickle cell disease and 14 cases of sickle cell trait were enrolled. In the present study male preponderance was seen, which was similar to other studies from central India [5, 6]. This could be due the gender-selective use of medical facilities and management of patients. Male to female ratio was 1.7:1. Most patients belonged to the age group of 5-12 years comprising 68.08% of total sickle cell disease patients. (34.04% in 5-8 years and 34.04% in 9-12 years of age group). In sickle cell trait 50% of patients in both gender belonged to the age group of 5-8 years. There was no statistically significant difference in gender in both groups.

In the present study, events requiring hospitalization was more commonly seen in the winter season (November to February). Lowering of temperature leads to increased viscosity of sickle blood resulting in stasis of the circulation in capillary beds. Apart from this, cold agglutinins and Cryoglobulins may contribute to the crises but their association still needs to be definitely established according to a study done in Jamaica [12]. Literature has mentioned that rainy season, low temperature or high wind speed and low moisture as contributing factors for vaso-occlusive emergency in sickle cell patients [9, 10].

Pain was the most widely recognized complain seen in 65.95% of sickle cell disease and 14.28% of sickle trait patients. Splenomegaly was seen in 27.65% of sickle disease and 14.28% of sickle trait. In the present study, isolated splenomegaly was more common than hepatomegaly as also mentioned in other studies [11]. Huge splenomegaly was noted in four patients, and corroborated with various studies from India [12]. Our cohort have, musculoskeletal pain in 40.54%, pain abdomen in 37.83%, generalized body ache in 18.91% and chest pain in 2.7% of cases. Subhramanyam *et al*. have reported musculoskeletal pain in 64%, pain abdomen in 35% and chest pain in 7% of cases [13].

Current study shows that, acute painful crisis (45.9%) was the most common cause for hospitalization, followed by severe anemia (39.34%) and infections (36.06%). In a study by Akar NA [17], vaso-occlusive crisis was the most common cause of hospitalization in SCD children. Another study from central India has reported severe anemia requiring blood transfusion as the most common cause of hospitalization in SCD children [18]. Study by Sinde S. showed respiratory infections in 37%, gastrointestinal infection in 9%, urinary tract infection in 2% and malaria in 9% cases [19]. The present study shows similar results and malaria was seen in 7.14% of cases. Previous studies have shown that SCT protects against severe forms and mild malaria infections, although the precise mechanism remains poorly understood [20].

There was no mortality of sickle cell patients presenting with painful crisis. However, if not properly and aggressively managed sickle cell patients may progress to severe hepatopathy and cardiac failure with end organ damage of kidney and other organs which may be life threatening. This study was a based upon the analysis of complications of sickle cell patients who were hospitalized but we need to carry out studies in a larger population which should include community based approach and these

patients should be kept on long term follow up to understand the course and nature of the disease manifestations.

Conclusion

In conclusion, our study revealed that morbidity events were common in males patients in 5-12 years of age groups, and is most commonly precipitated during the winter season. Vaso-occlusive emergency is the commonest indication in pediatric age group followed by anemia. Children with Sickle cell disease have a varied phenotypic expression both clinically and in hematological parameters. Parental counseling regarding regular use of hydroxycarbamide, folic acid supplementation, early treatment of fever and respiratory tract infections, vaccinations against capsulated organisms, use of simple analgesics, adequate hydration, avoiding high altitude Trecking and extremes of temperatures etc. should be done, so that they can prevent their children from having frequent Vaso-occlusive crisis. These patients should also be on regular follow up to assess adequate growth and development of the children and early intervention, if required before permanent organ damage occurs and to ensure a better quality of life.

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