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Original Article

Paediatrics Section

Clinical Correlates of Acute and Chronic Pulmonary Complications in Children with Sickle Cell Disease from Madhya Pradesh, India: A Cross-sectional Study

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ABSTRACT

Introduction: Sickle Cell Disease (SCD) is one of the most common hereditary haemoglobinopathies globally. Patients with SCD are at a high risk of pulmonary complications. However, there have been very few studies in literature regarding the spectrum of pulmonary involvement and its association with clinicotherapeutic parameters in Indian patients.

Aim: To study the incidence of acute and chronic pulmonary complications in children with SCD and to estimate the association of various risk factors with pulmonary complications.

Materials and Methods: The present observational cross-sectional study was conducted in the Department of Paediatrics, Mahatma Gandhi Memorial Medical College (tertiary care hospital) and Maharaja Yeshwantrao (MY) Hospital, Indore, Madhya Pradesh, India, from June 2021 to July 2022. A total of 100 patients with SCD below the age of 18 years attending sickle-thalassaemia Outpatient Department (OPD) and Inpatient Department (IPD) with pulmonary symptoms admitted were enrolled in the study. Clinical history, physical examination and laboratory findings were noted as per the preconstructed proforma. Data were statistically analysed with unpaired t-test and Pearson's Chi-square test.

Results: A total of 100 patients with SCD were enrolled and the mean age of the study subjects was 9.27±3.39 years. Nearly equal distribution of males (n=52) and females (n=48) were seen with male to female ratio of 1:1.08. Incidence of complications was seen very high in homozygous sickle disease (63%) followed by only 40% in Haemoglobin S (HbS) beta thalassaemia. Most common complication noted in the patients was Acute Chest Syndrome (ACS) (57.7%), followed by pneumonia (20%), sympneumonic effusion (15.6%) while only 6.7% had pulmonary hypertension. A statistically significant association (p-value <0.05) was found between compliance to Hydroxyurea therapy and frequency of Vaso-occlusive Crisis (VOC) episodes with pulmonary complications status.

Conclusion: In the present study, most frequent acute pulmonary complication noted was ACS followed by pneumonia and sympneumonic effusion. Frequency of VOCs episodes was significantly associated with increased risk of developing pulmonary complications.

Keywords: Acute chest syndrome, Anaemia, Haemoglobinopathy, Pneumonia

INTRODUCTION

The SCD is one of the most common hereditary haemoglobinopathies globally [1]. It is characterised by chronic haemolytic anaemia, recurrent painful acute and multiple complications. Affected individuals experience recurrent VOC, poor quality of life and a shortened lifespan. It requires acute care visits, frequent hospitalisations and contributes to increased morbidity and early mortality [2]. With advancing age, sustained haemolytic anaemia and repeated VOCs lead to chronic side-effects and various progressive end-organ complications [2].

Lung is one of the major organs affected by SCD being a common site of hypoxic and ischaemic injury and emboli from marrow infarcts/fat necrosis and is plagued with increased propensity for developing pneumonia [3]. ACS and complications associated with infection like pneumonia. ACS was defined as new radiodensity on chest radiography plus any two of the following symptoms: fever, respiratory distress, hypoxia, cough, and chest pain. Chronic complications could manifest as pulmonary hypertension and abnormalities in lung function characterised by airway obstruction, restrictive lung disease, abnormal diffusion capacity and hypoxaemia. The aetiology of pulmonary hypertension in patient with SCD is multifactorial, caused by chronic hypoxaemia, in-situ thrombosis, and parenchymal and vascular injury due to sequestration of sickle erythrocytes, fat embolisation and infection [3].

There is lack of data regarding acute and chronic pulmonary complications in paediatric population with SCD, especially in Indian scenario. Most of the studies [4,5] done are in adult population and from outside India [4,5]. Hence, the present study was conducted to estimate the incidence of acute and chronic pulmonary complications in children with SCD and to associate these complications with various clinical and therapeutic parameters.

MATERIALS AND METHODS

The present observational cross-sectional study was in the Department of Paediatrics, Mahatma Gandhi Memorial Medical College (tertiary care hospital) and MY Hospital, Indore, Madhya Pradesh, India, from June 2021 to July 2022. Study was carried out after taking permission from Institutional Ethics Committee (IEC clearance no: EC/MGM/Dec 21/06).

Inclusion criteria: Patients aged <18 years, with SCD, diagnosed on the basis of haemoglobin electrophoresis, attending sickle-thalassaemia OPD and IPD with respiratory symptoms (like cough, fever, chest pain, breathlessness) admitted in Paediatric ward and Intensive Care Unit (ICU) during the study period were included in the study.

Exclusion criteria: Patients with prior congenital heart diseases and lung diseases were excluded from the study.

Study Procedure

Demographic variables and family history was recorded for each patient. Detailed clinical history including age at presentation, age at

1st diagnosis, presenting complaints, VOC in the past, hydroxyurea intake was noted. Also, examination including anthropometric details (weight for age, height for age, weight for height, body mass index and mid upper arm circumference) and general physical examination, as per the preconstructed proforma, was done. Investigations like Complete Blood Count (CBC) for pretransfusion haemoglobin and White Blood Cells (WBC) counts, haemoglobin electrophoresis, serum ferritin levels were noted in all patients. The above parameters were taken based on previous studies, in which significant association was found between these risk factors and pulmonary complications [4,5]. For assessment of pulmonary involvement chest X-ray, Electrocardiogram (ECG), echocardiography (when needed to confirm the diagnosis) was done. Treatment was given as per the unit protocol, which included packed cell transfusion, if haemoglobin was less than 7 gm/dL. Intravenous antibiotics and supportive intravenous fluids and analgesia were given, if needed.

STATISTICAL ANALYSIS

Data was entered in to Microsoft excel spreadsheet and analysed using open sources software. Continuous data was expressed in the terms of mean and Standard Deviation (SD). Categorical data was expressed in form of proportions and percentage. Appropriate test of significance like unpaired t-test and Pearson's Chi-square test was applied wherever necessary and p-value <0.05 was considered statistically significant.

RESULTS

Total 100 patients with SCD were enrolled. Out of 100, 52 patients were males and 48 were females (male to female ratio of 1:1.08). All patients were diagnosed with SCD before five years of age with mean age in the study subjects being 9.27±3.39 years. In the present study, 19% patients were underweight, while 9% were severely malnourished. The mean pretransfusion haemoglobin was found to be 6.79±2.08 gm/dL [Table/Fig-1].

Parameters	Value (n)
Age (years) (Mean±SD)	
Age at enrollment (years)	9.27±3.39
Age at 1st diagnosis (years)	4.88±1.67
Gender	
Male	52
Female	48
Anthropometry	
Severe Acute Malnutrition (SAM)	9
Underweight	19
Stunted	14
Well-nourished	58
Type of disease	
Homozygous HbSS disease	55
HbS beta thalassaemia	25
Sickle cell trait	20
Pretransfusion haemoglobin (gm/dL) (Mean±SD)	6.79±2.08
Mean WBC count (cells/mm³) (Mean±SD)	10059.28±6775.49
Mean serum ferritin (ng/dL) (Mean±SD)	1153.39±1327.37

[Table/Fig-1]: Baseline characteristics of children with Sickle Cell Disease (SCD) in the study (n=100).
WBC: White blood cells

The most common presenting symptom was fever (n=36) followed by chest pain (n=24) and cough (n=20). While less common symptoms were dyspnoea (n=9) and palpitations (n=4) [Table/Fig-2]. Among patients of ACS, 77% (n=20) had fever, 54% (n=14) had cough while 42% (n=11) had chest pain. The most common acute complication seen in the present study was ACS (n=26, 57.7%), of which (n=14, 70%) patients belonged to 6-10 years age group. And most common chronic complication seen here was pulmonary hypertension in 3 (6.7%) patients and all of them were seen in older children above 10 years of age [Table/Fig-3]. In the present study, 35 (63.6%) cases of homozygous HbSS disease developed pulmonary complications, while none of the patients with sickle cell trait had any complications [Table/Fig-4]. Most common radiological findings were consolidation with air bronchogram 20 (20%), patchy infiltrates in the lung fields 15 (15%) and sympneumonic effusion 7 (7%) [Table/Fig-5].

Symptoms	n (%)
Fever	36 (36)
Chest pain	24 (24)
Cough	20 (20)
Dyspnoea	9 (9)
Palpitations	4 (4)

[Table/Fig-2]: Distribution of symptoms in children with Sickle Cell Disease (SCD) with pulmonary complications (N=100).

Complications	<5 years (n=5) n (%)	6-10 years (n=20) n (%)	10-18 years (n=20) n (%)	Total (n=45) n (%)
Acute				
ACS	2 (40)	14 (70)	10 (50)	26 (57.7)
Pneumonia	2 (40)	3 (15)	4 (20)	9 (20)
Sympneumonic effusion	1 (20)	3 (15)	3 (15)	7 (15.6)
Chronic				
Pulmonary hypertension	0	0	3 (15)	3 (6.7)

[Table/Fig-3]: Distribution of complications in different age groups (n=45).
Values presented as n (%); ACS: Acute chest syndrome

Complications	Homozygous HbSS disease (n=55) n (%)	HbS beta thalassaemia (n=25) n (%)	Sickle cell trait (n=20) n (%)
Acute			
ACS*	18 (32.7)	8 (32)	0
Pneumonia	8 (14.5)	1 (4)	0
Sympneumonic effusion	6 (10.9)	1 (4)	0
Chronic			
Pulmonary hypertension	3 (5.5%)	0	0
Total	35 (63.6)	10 (40)	0

[Table/Fig-4]: Distribution of complications according to type of Sickle Cell Disease (SCD) (n=45).
ACS: Acute chest syndrome

Chest X-ray findings	Homozygous HbSS disease (n=55) n (%)	HbS beta thalassaemia (n=25) n (%)	Sickle cell trait (n=20) n (%)
Air Bronchogram with consolidation (n=20)	15 (75)	5 (25)	0
Patchy Infiltrates without air bronchogram (n=15)	11 (73)	4 (27)	0
Sympneumonic effusion (n=7)	6 (85.7)	1 (14.3)	0
Cardiomegaly with prominent pulmonary vasculature (n=3)	3 (100)	0	0
Total patients with pulmonary complications	35	10	0

[Table/Fig-5]: X-ray findings among patients with pulmonary complications.
Values presented as n (%)

There was significant association between frequency of VOC and pulmonary complications (p-value=0.004). Sixteen (61%) patient

of ACS, five out of nine patients of pneumonia (55%), four out of seven patients of sympneumonic effusion (57%) and one patient of pulmonary hypertension had history of >3 VOCs in the preceding one year. A total of 39 (62%) of the patient with >3 VOC in the preceding year had complications. A higher proportion of patients who did not take hydroxyurea developed pulmonary complications i.e., 32 out of 47 (68%), while only 13 out of 57 (24.5%) patients who were taking hydroxyurea developed pulmonary complications. The mean WBC value 12791.11 cells/mm^3 for patient with complications was significantly higher (p-value=0.001) than patient without complications (mean WBC=7824.15 cellls/mm^3). Thus, indicating many of the complications were of infective aetiology. On comparison of mean serum ferritin value among patients with or without pulmonary complications, statistically significant higher values of serum ferritin were seen in patient with pulmonary complications (p-value=0.001) [Table/Fig-6].

Parameters	Patient with pulmonary complications (n=45), n (%)	Patient without pulmonary complications (n=55), n (%)	p-value
Electrophoresis			
HbSS disease	35 (63.6)	20 (36.4)	**0.001**
HbS beta thalassaemia	10 (40)	15 (60)	
Sickle cell trait	0	20 (100)	
VOC in the past one year			
0-3	19 (38)	39 (62)	**0.004**
>3	26 (62)	16 (38)	
Hydroxyurea intake			
Yes	13 (24.5)	40 (75.5)	**0.001**
No	32 (68)	15 (32)	
Mean haemoglobin (gm/dL) (Mean±SD)	6.41±1.74	7.10±2.28	0.097
Mean WBC (cells/mm^3)	12791.11±8168.23	7824.15±4300.16	**0.001**
Mean ferritin (ng/dL) (Mean±SD)	1647.78±1536.11	748.49±968.08	**0.001**

[Table/Fig-6]: Risk factors associated with pulmonary complications.
VOC: Vaso-occlusive crisis; Pearson's Chi-square test and unpaired t-test was applied ; The p-value in bold font indicates statistically significant values

DISCUSSION

The mean±SD age of patients was found to be 9.27±3.29 years. The results of the present study were in concurrence with the study done by Neonato MG et al., who studied 299 patients of SCD, the mean±SD age at evaluation was 10.1±5.8 years [6]. The mean±SD age of diagnosis in the present study patients was 4.88±1.67 years. Similar results were seen in an earlier study done by Brown BJ et al., in which it was found that mean age at diagnosis in developing country was two years [7].

The most common acute complication seen in the present study was ACS (n=26, 57.7%), of which maximum 14 (70%) patients were in the 6-10 years age group. It has been suggested by Koumbourlis AC that pulmonary complications develop early in the disease [8]. Similar results were reported by Paul RN et al., Meier ER and Miller JL, stating that ACS is a life-threatening complication of SCD with peak incidence in early childhood [5,9]. In the present study, it was found that all the cases of chronic pulmonary complications (pulmonary hypertension) belonged to age group >10 years. This can be attributed to increased incidence of complications in SCD with the age as stated by Miller AC and Gladwin MT [10]. Patients are at risk for a progressive vasculopathy characterised by systemic and pulmonary hypertension, endothelial dysfunction, and proliferative changes in the intima and smooth muscle of blood vessels [11,12]. Thus, with increasing age, the incidence of chronic end-organ complications increased.

Most of the enrolled patients in the present study was of homozygous sickle disease (55%) followed by HbS beta thalassaemia (25%) and least were of sickle cell trait (20%). Similar results were reported in a study done by Adekile AD et al., [13]. In which the most common genotype among 396 patients was homozygous sickle disease (62.1%) followed by HbS beta thalassaemia (34.8%). In the present study, 63.6% of the patients with homozygous sickle disease had pulmonary complications, while none of the patient with sickle cell trait had any complication. Similar results were reported in the study by Saraf SL et al., [14]. They suggested that there is higher prevalence of pulmonary function test abnormalities along with elevated tricuspid regurgitant velocity (pulmonary hypertension) in patient with homozygous sickle disease or HbS beta thalassaemia in comparison to patient with HbS Beta$^+$thalassaemia or sickle cell trait. Similarly higher incidence of ACS in homozygous sickle disease or HbS beta thalassaemia was reported by Paul RN et al., [5]. Higher rate of haemolysis and low haemoglobin is the cause.

In the present study, a significant positive association (p-value=0.004) was seen between frequency of VOCs in the past and pulmonary involvement (ACS or pneumonia). Similar results were seen in a large cross-sectional study done by Paul R et al., ACS or pneumonia were found to be independently associated with >3 VOCs in the preceding one year [4]. Bailey M et al., reported a hazard ratio of 5.33 in patients of ACS with history of >3 VOCs in the preceding one year [15]. The reason can be acute haemolysis following VOC contributing to the development of lung injury. Higher levels of free heme (byproduct of haemolysis) are associated with increased risk of developing ACS. This observation is supported by the recent findings of a sickle cell mouse model suggesting that extracellular hemin may contribute to ACS pathogenesis through toll like receptor [16].

A statistically significant association was found between hydroxyurea intake and pulmonary complications status. A higher proportion (68%) of patients who did not take hydroxyurea developed pulmonary complications, while only 24.5%, patients who took hydroxyurea developed complications (p-value=0.001). This protective effect of hydroxyurea in prevention of pulmonary complications was similar to that reported in a study by Montalembert M et al., in which 68% reduction in episodes of ACS was seen with regular use of hydroxyurea [17]. Another study done by Ataga KI et al., reported 65% cases of pulmonary hypertension in patients who were not on hydroxyurea treatment versus 35% cases of pulmonary hypertension in patients who were on hydroxyurea treatment [18]. Hydroxyurea was associated with statistically significantly lower rates of initial and recurrent episodes of pain, ACS, need of blood transfusions and hospitalisation. Though mild myelosuppression is a known side-effect, no increased risk of bacteraemia or serious infection was noted with the use of hydroxyurea in the present study [18].

The mean value of WBC i.e., 12791.11 cells/mm^3 for patients with complications was significantly higher than for patients without complications (mean WBC=7824.15 cells/mm^3). Thus, indicating many of the present study complications were of infective aetiology. Highest levels of mean WBC were found in cases of pneumonia followed by sympneumonic effusion and ACS, respectively. Low levels of WBC were seen in chronic pulmonary complications like pulmonary hypertension. This was comparable with the study done by Paul RN et al., which showed raised mean WBC of 11,400 cells/mm^3 in patients with acute pulmonary events [5]. On comparison of various similar studies done outside India, it was found that, though the mean age of patients was comparable but the incidence of ACS was lower than in the western world [Table/Fig-7] [5,6,19].

Name of author	Neonato MG et al., [6]	Vinchisky EP et al., [19]	Paul RN et al., [5]	Current study
Place of study	Paris, France	California San Francisco Oakland, USA	Washington Michigan Chicago, USA	Madhya Pradesh, India
Year of study	1987-1997	1993-1997	2006-2010	2020-2021
Sample size (N)	299	538	503	100
Mean age (years)	10.1	13.8	13	9.27
>3 VOCs in past one year (%)	-	80	24	62
Mean WBC counts cells/mm^3	-	23000	11400	12791
Mean ferritin (ng/dL)	-	-	348	1647
Incidence of ACS n (%)	132 (44)	538 (100)	246 (49)	26 (26)

[Table/Fig-7]: Comparison among various studies on sickle cell children with pulmonary events [5,6,19].

Limitation(s)

Modalities like pulmonary function tests were not available due to Coronavirus Disease (COVID) times for better understating of pulmonary complications. It was a single centre study with small sample size. Therefore, the present study's findings might have limited generalisability to other healthcare settings.

CONCLUSION(S)

The most common pulmonary complications seen in the present study was ACS followed by pneumonia and sympneumonic effusion, with very few cases of pulmonary hypertension, respectively. The present study highlights the positive association of mean ferritin, mean WBC count and VOC episodes with pulmonary complications. Hence, it would be prudent to screen patients with SCD by using various clinico radiological tests for early detection of any acute or chronic pulmonary complications and to institute their early treatment.

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