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Acute morbidity pattern and organ dysfunction in hospitalized children with sickle cell disease-A single center experience.

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Abstract

Background: The most prevalent hemolytic anemia-causing single-gene disorder is Sickle Cell Disease (SCD). In a paediatric population, it is one of the often occurring reasons of repeated hospitalization, morbidity, and mortality. Limited information is available on the acute morbidity pattern and organ dysfunction in younger Indian children with SCD.

Methods: This prospective observational study was carried out in the tertiary care centre between January 2018 and June 2019. All of the patients ranged in age from six months to twelve years. In the study, cases of SCD that had previously been identified and had an SS pattern detected by High-Performance Liquid Chromatography (HPLC) or Hb electrophoresis were assessed for acute morbidity and multiple organ involvement.

Results: 178 children with SCD who had been identified by HPLC were included in the study. 108 of the children, or 60.68% of the total population, were between the ages of 5 and 10. Pain was the most prevalent presenting symptom, occurring in 123 (69.10%) instances. Severe pallor in 108 instances (60.67%) and splenomegaly in 48 cases (26.97%) were the other common presenting symptoms. Hospitalisation was brought on by a Vaso-Occlusive Crisis (VOC) in 114 (64.04%) of the patients, severe anaemia in 104 (58.42%), and acute febrile illness in 80 (44.94%). Out of the 178 patients admitted to the hospital for acute morbid events, it was found that 64 (35.95%) had multiple organ dysfunction. Hepatobiliary involvement was observed in 27 (42.18%) cases, splenic involvement in 12 (18.75%) cases, neurological involvement in 16 (25%) cases, Acute Chest Syndrome (ACS) involvement in 7 (10.93%) cases, and cardiac involvement in 2 (3.12%) instances, among other organs. In six (3.37%) cases, mortality was noted. One case of acute chest syndrome, two cases of stroke and seizure, two cases of sequestration crisis, one case of cardiac dysfunction and severe anaemia, and two cases each of stroke and seizure all resulted in death. 172 patients, or 96.63% of the total, were discharged.

Conclusion: The most frequent symptom in children under 18 is Vaso-Occlusive Crisis (VOC). A statistically significant relationship between organ failure and age in years was discovered (p=0.0181). The correlation between blood transfusions and hepatobiliary involvement was established, and the anticipated P-value was shown to be statistically extremely significant (p=0.0001).

Keywords: Sickle Cell Disease (SCD), Vaso Occlusive Crisis (VOC), Acute Chest Syndrome (ACS), High Performance Liquid Chromatography (HPLC).

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Introduction

Sickle Cell Anemia (SCA) is an inherited disorder associated with significant morbidity and mortality [1]. Although children with SCA can remain healthy for some time, these periods are interrupted by severe health crises that require hospital admission [2]. SCD is a common genetic disorder. It is characterized by chronic hemolytic anemia and vaso-occlusive crises arising from widespread vascular occlusion by sickled red blood cells, leading to multiple organ infarctions [3]. In India, the carrier rate of HbS varies among states, communities, and ethnic groups, with an average prevalence of 4.3% (range 0%-44.0%). It is found predominantly in Vidarbha (Northern Maharashtra), Madhya Pradesh, Orissa, Chhattisgarh, Gujarat, and also in some areas of Andhra Pradesh, Tamil Nādu, Kerala, and Karnataka. Previously, it was believed that the sickle cell gene in India was found predominantly in tribal communities.

However, later studies have shown an equally high prevalence in non-tribal communities in central and eastern India [4]. The

highest prevalence of HbS in the world is in sub-Saharan Africa, followed by the Arabian Peninsula and the Indian subcontinent [5]. Improved knowledge and successful primary public health prevention strategies have positively impacted the childhood survival of SCD patients, transforming it into a less chronic disease. Nonetheless, progressive deterioration of organ function and end-organ damage is inevitable and appears to be irreversible [6-8]. Limited information is available on the acute morbidity pattern and organ dysfunction in younger Indian children with SCD. In order to assess acute morbidity patterns and organ dysfunction in SCD patients, the current study was carried out.

Materials and Methods

Study design

This is a prospective observational study that was carried out between January 2018 and June 2019 in the tertiary care centre to assess acute morbidity patterns and organ dysfunction in children with SCD there. The study was given go by the participating hospitals' Institutional Ethical Council (IEC). 178 participants who had previously been diagnosed with SCD and an SS pattern (on HPLC) made up the study cohort.

Inclusion criteria

The inclusion criteria were as follows:

- Subject age group from 6 months to 12 years;
- Both the male and female genders; and
- All previously diagnosed cases of SCD children with SS pattern (that is, HPLC or Hb electrophoresis suggestive of SCD SS pattern).

Exclusion criteria

The exclusion criteria were as follows:

- Subject diagnosed with congenital heart disease, congenital anomalies, chromosomal defect, inborn error of metabolism, musculoskeletal involvement, and other hemoglobinopathies;
- Subject with diagnosed malignancy;
- Subject with a chronic medical condition such as tuberculosis, HIV/AIDS, renal diseases or others;
- Subject with an obvious physical disability such as cerebral palsy and post-traumatic physical disability; and
- Subject with declined informed consent or assent.

Data collection

All subjects suffering from SCD were selected for the study after securing informed consent from them or their parents. Data was collected using a pre-formed questionnaire consisting of two parts. The first part included socio-demographic details such as age, gender, occupation, religion, education, socio-economic status (according to the modified Kuppuswamy socioeconomic status scale updated for year 2018), while the second part consisted of the clinical examination, laboratory findings, and outcomes. The questionnaire was validated by being translated into the local language and reviewed by a group of experts. Events such as acute painful crisis, dactylitis, severe anemia, sequestration, acute febrile illness, and stroke were defined as per standard criteria [9].

SS patterns on HPLC were used to identify patients of SCD that had been officially diagnosed. The immunisation status, hydroxyurea use status, and blood transfusion status of diagnosed individuals were all determined through thorough clinical examinations. It was also investigated how frequently they were admitted. Organ dysfunction in SCD subjects hospitalized for acute morbidity was evaluated based on predefined clinical criteria adapted from Ballas et al., [10]. Accordingly, participants were divided into different categories of organ dysfunction, and associations between subjects with organ dysfunction, frequent blood transfusions, acute events, and outcomes were found.

Statistical analysis

Data were coded and analysed using Stata 10.1 (2011). The correlation between continuous variables and organ dysfunction was evaluated with two independent sample t-tests. P-value<0.05 was considered statistically significant.

Results

A total of 178 patients who were enrolled had already been given the SCD (SS pattern) diagnosis by HPLC and were being treated for acute morbid episodes in paediatric wards of tertiary medical facilities [11,12]. The male to female ratio of the 178 children investigated was 1.37:1, with 103 (58%) males and 75 (42%) females. The majority of children were found to be in the 5 to 10 year age range (60.93%), followed by the youngest age group (25.28%). shown in Table 1. In a research by Salman et al., [13] the mean age was 7.97 ± 3.65 years, with 56.88% of the participants being male and 43.12% female, with ages ranging from 9 months to 14 years. Similar results were found in studies conducted by Jain et al., [14] and Patel et al., [15].

Age in years	Total (N=178)		Male (N=103)		Female (N=75)	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
01-05	45	25.28%	33	32.04%	12	16%
05-10	108	60.68%	55	53.40%	53	70.67%
10-12	25	14.04%	15	14.56%	10	13.33%
Total	178	100%	103	100%	75	100%

Table 1. Age and gender-wise distribution of study subjects.

In the present study, pain was the most prevalent presenting complaint in 123 (69.10%) cases, followed by 108 (60.67%) cases of pallor, 80 (44.94%) cases of fever, 48 (26.97%) cases of splenomegaly, 46 (25.84%) cases of cough, 33 (10.54%) cases of icterus, 5(2.80%) cases of hemiparesis, and 11 (6.17%) cases of seizures. According to a study by Patel et al., [15] pain (65.95%) was the most prevalent symptom among SCD patients, followed by fever (36.17%) and cough (17.02%). The two most typical symptoms were pallor (46.7%) and splenomegaly (27.5%) (Table 2).

The most common event responsible for hospitalisation was found to be a VOC in 114 (64.04%) cases, followed by severe anaemia in 104 (58.42%) cases, acute febrile illness in 80 (44.94%) cases, stroke and seizure in 16 (8.98%) cases, acute chest syndrome in 7 (3.93%) cases, and sequestration in 6 (3.37%) cases (Table 3). In addition, Salman et al., [13], Adekile et al., [16], Jaiyesimi et al., [17], and Brown et al., [18] discovered that acute painful crises was the most common cause of hospitalization [19].

In the study mentioned in Table 4, hepatobiliary dysfunction was found in 27 (42.18%) of those with organ dysfunction, followed by Central Nervous System (CNS) dysfunction in 16 (25%), splenic dysfunction in 12 (18.77%) cases, pulmonary dysfunction in 7 (10.93%) cases, and cardiac dysfunction in 2 (3.12%). Bokade et al., [20] found similar results in their investigation. Since there was a significant correlation between organ dysfunction and age measured in years, it may be deduced that as people age, organ dysfunction develops and becomes clinically obvious. The relationship between organ malfunction and years of age was determined to be statistically significant (p=0.0181) and is shown in Table 5.

Presenting clinical feature	No. of cases (N=178)	Percentage (%)
Pain	123	69.10%
Fever	80	44.94%
Pallor	108	60.67%
Icterus	33	10.54%
Hemiparesis	5	2.80%
Seizures	11	6.17%
Cough	46	25.84%
Splenomegaly	48	26.97%
Hepatomegaly	24	13.48%
Vomiting/Diarrhea	7	3.93%

Table 2. Distribution of cases according to presenting clinical feature.

Acute event	No. of cases (N=178)	Percent (%)
Painful event (VOC)	114	64.04%
Severe anemia	104	58.42%
Acute febrile illness	80	44.94%
ACS	7	3.93%
Stroke/seizure	16	8.98%
Sequestration crisis	6	3.37%

Table 3. Distribution of cases according to acute events responsible for hospitalization.

Organ dysfunction	Findings	No. of cases (N=64)	Percentage (%)
Hepatobiliary (N=27)	Cholelithiasis	15	42.18%
	Cholecystitis	7	
	V. hepatitis	5	

Splenic (N=12)	*S.infarct* and ASSC	4	18.77%
	S.micro-abscess and ASSC	8	
Neurological (N=16)	Stroke	5	25%
	Seizure	11	
Pulmonary (N=7)	ACS	7	10.93%
Cardiac (N=2)	Cardiomyopathy	2	3.12%
Total (N=64)		64	100%

Table 4. Distribution of cases according to different types of organ dysfunction.

Organ dysfunction	Mean	SD	t-value	p-value
Yes	8.26	2.62	2.3856	0.0181, S
No	7.23	2.83		

Table 5. Association of organ dysfunction with age in years in study subjects.

According to Table 6 findings, there is a direct correlation between organ dysfunction and the number of blood transfusions needed within the previous year (>3) that is statistically significant (p=0.001, HS). When compared to 114 participants without organ dysfunction, 42 of the 64 subjects with organ dysfunction had received more than three blood transfusions in a year. According to the observations mentioned above, the chance of having organ dysfunction increases as the frequency of blood transfusions increases. With a mean age and SD of 8.26 ± 2.62 years, the current study found a positive correlation between organ dysfunction and age in years. This finding implies that organ dysfunction develops with age and becomes clinically obvious. It was shown that there was a statistically significant correlation between organ dysfunction and years of age (p=0.0181). Blood transfusions and hepatobiliary involvement were shown to be correlated, and the expected P-value was found to be statistically extremely significant (p=0.0001).

Discussion

This study included 178 patients who had already been given the diagnosis of SCD (SS pattern) by HPLC or Hb electrophoresis and were admitted to paediatric wards of tertiary medical facilities for acute morbid episodes. Chronic hemolysis caused by the early decomposition of fragile and weakly deformable red blood cells is a hallmark of the genetic condition SCD. It is brought on by the existence of sickle haemoglobin, which develops when glutamic acid at position 6 of its chains is replaced by valine [11]. In addition to prolonged hemolysis, ischemic changes brought on by vascular blockage by masses of sickled red cells are responsible for other symptoms of sickle cell anaemia. Children with the condition generally have intermittent episodic experiences, also known as "crises" [12]. Haemoglobin SS children might have chronic anaemia as well as acute anemia-related conditions include VOC, dactylitis, sequestration, hyper hemolytic crisis, Acute Chest Syndrome (ACS), aplastic crisis, priapism, and cerebrovascular accidents. Chronic side effects can raise your risk of getting sick, have strokes, have kidney damage, have liver problems, and have slower growth. A significant rate of morbidity and mortality result from these clinical symptoms.

Male to female ratio was 1.37:1 among the 178 youngsters in the research, with 57.87% of them being boys and 42.13%being girls. With ages ranging from 9 months to 14 years old, 56.88% of the participants in a study by Salman et al., [13] were men and 43.12% were women. There were 7.97 ± 3.65 years of average age. Jain et al., [14] and Patel et al., [15] research both produced similar findings. Following severe anaemia (58.42%) and acute febrile illness (44.94%), VOC (64.04%) was the most common reason for hospitalisation. In the study conducted by Salman et al., [13], acute painful crises were also the most common cause of hospitalisation. ACS (8.02%), Acute Splenic Sequestration Crisis (ASSC) (6.32%), and infection (9.28%) were the next three causes of death.

	No. blood transfusion (In last one year)		t-value	p-value
Organ dysfunction (N=64)	>3	≤ 3		
Yes	42	43	12.7935	<0.001, HS
No	22	71		

Table 6. Association of organ dysfunction with number of blood transfusion required in last one year.

Acute painful crises were similarly the most common reason for inpatient hospitalisation of SCD patients in the current investigation. The results of investigations carried out in Kuwait by Adekile et al., [16], Jaiyesimi et al., [17], and Brown et al., [18] (61.5%) are supported by this result. However, Jain et al., [14] evaluated hospitalised children under the age of five in their study and discovered that acute febrile illness (31%) was the most frequent morbid event, followed by severe anaemia (30%) and acute painful events (20%), for age with SCD for morbid events leading to hospitalisation and observed hospitalisation. In our analysis, the conditions more prevalent in older adults were stroke (0.6%), splenic sequestration crisis (4%), acute chest syndrome (3.3%), and hand-foot syndrome (11%).

Acute painful crisis was listed as the leading reason for hospitalisation by Patel et al., [15], followed by severe anaemia (39.34%) and infections (36.06%). According to a study by Shinde et al., [19], respiratory infections accounted for 37% of cases, gastroenteritis for 9%, urinary tract infections for 2%, and malaria for 9%. Additionally, it was noted that the abdomen (29.27%) and extremities (39.83%) were the two most typical pain sites. Back pain (6.50%) and pain in numerous areas (18.70%) were also noted in the individuals.

In the study by Salman et al., [13], the extremities were also the most often affected areas by pain, and 30.7% of the patients reported discomfort at more than one location. Similar to how Wojner-Alexandrov et al., [12] in the USA discovered that the extremities were the most frequent source of pain, Jaiyesimi et al., [17] in Oman observed that 45% of hospitalised patients with SCD had pain in their limbs. Of the 178 patients hospitalised for acute morbidity in the current study, 64(34.95%) had organ involvement. Out of the 64 instances with organ involvement, hepatobiliary involvement was seen in 27(42.18%) cases, splenic involvement in 12, neurological involvement in 16, pulmonary involvement in 7, and cardiac involvement in 2. There were 7 (25.93%) cases of cholecystitis, 15 (55.56%) cases of cholelithiasis, and 5 (18.51%) cases of viral hepatitis out of the 27 (42.18%) cases with hepatobiliary involvement in children aged 5 to 10. Similar findings were seen in a research by Bokade et al., [20], who reported viral hepatitis in 36.47% of cases, cholelithiasis in 28.24% of cases, and cholecystitis in 27.06% of cases. Ajani et al., [21] observed that the prevalence of cholelithiasis in children with sickle cell anaemia in steady state was 4.8%. Similar outcomes were discovered by Allali et al., [22], who reported the most prevalent finding of cholelithiasis, in 25% of cases, which led to systematic screening and elective cholecystectomy in the case of gallstones.

There were also splenic abscesses in 8 (66.66%) instances and splenic infarcts in 4 (33.33%) cases out of the aforementioned 64 patients with organ involvement, while splenic involvement was seen in 12 (18.75%) cases. Three of their patients, who were 8, 10, and 14 year's old, experienced significant splenic infarction, according to a study by Al-Salem [23]. All of them exhibited splenomegaly, and there was no immediately apparent cause of the infarction. Of the 64 cases where an organ was involved, neurological involvement was seen in 16 (25%) of the patients (5-10 years old), manifesting as seizures in 11 (68.75%) cases and ischemic strokes in 5 (31.25%).

In the study of Earley et al., [24], it was determined that 18 of these children's had ischemia infarction and 17 had intracerebral haemorrhage. SCD was the most typical contributor to ischemic strokes (39%), which led to the conclusion that SCD contributes disproportionately heavily to paediatric stroke in the population studied. Sickle cell anaemia (SS) patients had a prevalence rate of 4.1% and an incidence of 0.61 per 100 patient-years in a study by Ohene-Frempong et al., [25] to determine the rates and risk factors for cerebrovascular accidents in SCD.

Age, with a mean of 8.26 years and 2.62 years, was found to positively correlate with organ dysfunction. According to the aforementioned fact, organ failure occurs and becomes clinically evident as people age. Age and organ dysfunction were discovered to be statistically significantly correlated ($p=0.0181$). Bokade et al., study produced findings that were similar. When hepatobiliary involvement and blood transfusions were correlated, it was discovered that, of the 85 participants who had hepatobiliary involvement, 12 had gotten fewer than three blood transfusions in the preceding year and 73 had received more than or equal to three. Out of 110 people who were healthy and had no hepatobiliary disease, 106 had received no more than three blood transfusions in the previous year, whereas 4 had received three or more. The calculated P-value was discovered to be extremely statistically significant ($p=0.0001$).

Six (3.37%) of the 178 individuals with acute SCD episodes were found to have died. Sequestration crisis cases saw two fatalities, stroke and seizure cases saw two deaths, acute chest syndrome cases saw one death, and severe anaemia cases saw one death. The remaining 172 cases (96.63%) were discharged.

There were certain limitations on this study. An isolated context with a small sample size and organ damage risk factors unique to the local population may not be generalizable to other populations. Additionally, no patients with renal dysfunction were included in the study.

Conclusion

In age groups of 5 to 10 years, morbidity was prevalent, and Vaso-Occlusive Crisis (VOC) was the most frequent symptom in the paediatric age group, according to our study. It was determined that there was a statistically significant correlation between organ dysfunction and years of age ($p=0.0181$). Blood transfusions and hepatobiliary involvement were found to be correlated, and the predicted P value was discovered to be statistically very significant ($p=0.0001$).

Reducing the frequency of crises would enhance life expectancy, delay long-term consequences, and improve quality of life. Immunisation, a healthy diet, folic acid and zinc supplements, and hydroxyl urea may all help to lower the frequency of infections, blood transfusions, and hospitalisation,

which would delay the beginning of organ issues. Additionally significantly lowering the number of infants born with the condition will be genetic counseling and screening.

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