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Comprehensive Exploration of Hepatobiliary Manifestations in Sickle Cell Disease: Hematological and Biochemical Profiles

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Abstract

Introduction- Sickle Cell Disease (SCD) is a hereditary disorder with origins debated between migratory populations in India and equatorial Africa, spreading globally through trade routes. Liver involvement in SCD is frequent, marked by sickling, sinusoidal blockage, and hepatocyte abnormalities. Despite its significance, comprehensive data on liver function in SCD are lacking. This study conducted a one-year cross-sectional examination at MKCG Medical College and Hospital, focusing on pediatric patients with positive sickling tests. The study aimed to unravel hepatobiliary manifestations alongside hematological and biochemical profiles, addressing the current gap in comprehensive data. **Results**: A total of 210 cases showed a predominance in the 6-10 age group, with females outnumbering males. Chief complaints included pallor, weakness, jaundice, fever, and pain. Hepatic complications, notably benign hyperbilirubinemia, acute hepatic crisis, and cholelithiasis, were prevalent. Gastrointestinal system involvement was predominant, and ultrasonographic findings indicated splenomegaly and hepatosplenomegaly. Age-wise differences in complications and outcomes were observed, with 5.7% mortality, higher in SS than AS varieties. **Discussion**:The study highlighted the age distribution, clinical symptoms, and complications, emphasizing the need for early detection and comprehensive care. Complications were more prevalent in SS than AS groups, and mortality was higher in SS. Laboratory parameters were consistent with previous studies, underscoring the importance of a multidisciplinary approach for diagnosis and treatment.**Conclusion**: Complications in SCD increase with age, necessitating frequent hospital reporting. Hepatic complications, including benign hyperbilirubinemia, acute hepatic crisis, and cholelithiasis, were prevalent, stressing the importance of early detection and comprehensive care. Increased awareness and understanding of hepatobiliary complications, risk reduction, monitoring, and early intervention are crucial to decrease mortality in SCD.

Keywords: Sickle cell disease, Hospital-based, Genetics, Haemoglobinopathy.

Introduction:

The origins of sickle cell disease remain a subject of debate, with suggested connections to both migratory aboriginal populations in India and equatorial Africa. Its subsequent dissemination into the Mediterranean, the Middle East, and widespread presence across Northern and Southern regions of the Western hemisphere is closely linked to evolving trade routes.1-2 In 1910, Dr. J. B. Herrick initially reported sickle cell disease, describing elongated and sickle-shaped red blood cells in a West Indian student. Professor Nalbandian's remark, "A disease more dreaded than cancer," underscores its severity. Pauling's 1949 work identified abnormal hemoglobin, and in 1952, Dunlop and Majumdar detailed sickle cell anemia in India. Western Odisha's sickle cell prevalence was first noted by Nanda & Praharaj in 1967, revealing a 15.1% frequency of the HbS gene.3-4 Notably, the sickle gene is not confined to tribal communities but extends across societal groups, with higher prevalence in certain caste Hindus.5-6 The disease's manifestation involves sickle or crescent-shaped red cells during anoxic states due to hereditary abnormalities. Sickle cell disease (SCD), an autosomal recessive disorder, stems from a point mutation in the β-globin gene, resulting in the formation of HbS (Sickle Hb.) that polymerizes during deoxygenation, causing sickle-shaped RBCs.6-7

Sickle cell anemia and its variants manifest as inherited disorders characterized by chronic hemolytic anemia, frequent bacterial infections, and vasoocclusive episodes leading to ischemia, infarction, and fibrosis. The spectrum ranges from severe symptoms in children to asymptomatic adults. Liver involvement is common, marked by sickling, sinusoidal blockage, hepatocyte fatty degeneration, and atrophy.8

The liver's role in sickle cell disease is vital, with associated abnormalities noted in 27% of affected children, exhibiting elevated serum bilirubin levels.4 Hepatic dysfunction is recurrent, and viral hepatitis complicates the condition.9 Specific syndromes include hepatic sequestration, acute viral hepatitis, cholelithiasis with cholecystitis, cirrhosis, hepatic crisis/acute hepatic failure, and intrahepatic cholestasis.10-12 Notably, these abnormalities intensify during vasoocclusive crises.

Despite this understanding, recent comprehensive data on liver function in sickle cell disease are lacking. This study aims to bridge this gap, exploring hepatobiliary manifestations alongside hematological and biochemical profiles. As sickle cell disease emerges as a global public health concern, this research strives to enhance recognition and understanding of its multifaceted impact on health and well-being.

Methodology

The cross-sectional study was carried out at the MKCG Medical College and Hospital, for a period of 1 year. The study was carried out in the outpatient and inpatient departments, focusing exclusively on children showcasing positive sickling test results.

STUDY DESIGN

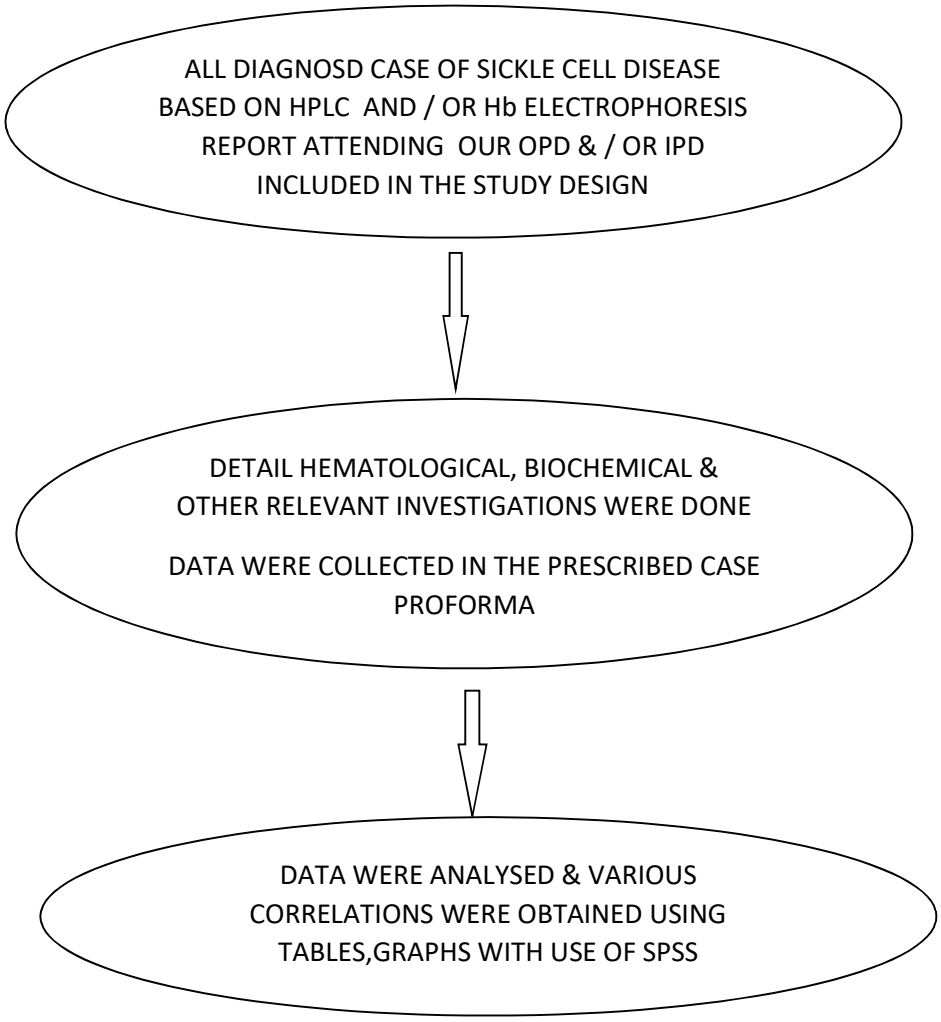

Figure 1: Flow Chart For The Study

The eligibility criteria for inclusion in this study was defined. Children exhibiting homozygous sickle cell hemoglobinopathy (HbSS) and heterozygous sickle cell hemoglobinopathy (HbAS) were included in the study. To ensure specificity and isolate the unique characteristics of sickle cell disease, individuals with double heterozygous conditions (e.g., HbSC, HbSF) and those grappling with alternative forms of hemolytic anemia were deliberately excluded from the cohort.

The participants were identified, with detailed histories, and clinical examinations based on a specially designed case proforma. To ensure a holistic view of each case, a comprehensive case study design was employed, allowing for a nuanced understanding of the medical conditions under scrutiny. The laboratory dimension of the study was hemoglobin estimation, a key quantitative measure of abnormal hemoglobin levels, through Sahli's acid haematin method (Wintrobe, 1967). Total leucocyte counts, crucial in unraveling the broader immune context, were determined using Turk's solution and Thomas diluting pipette in a conventional method.

Result

The age distribution of the 210 cases indicated a predominance in the 6 to 10 years age group (47.1%), followed by 11 to 14 years (36.2%), and the lowest in those under 5 years (16.7%). Among the sickle cell children, females (56.2%) outnumbered males (43.8%). Hemoglobin electrophoresis revealed 89% SS variety and 11% AS variety among the 210 cases.

Table 1 Sociodemographic And Clinical Characteristics

		Number	Percentage
Age Group	1-5	35	16.70%
	6-10	99	47.10%
	11-14	76	36.20%
Gender	Male	92	43.80%
	Female	118	56.20%
Hb electrophoresis	SS	187	89%
	AS	23	11%
Chief complaints	Pallor	208	96.20%
	Jaundice	103	49%
	Fever	82	39%
	Bone pain	65	31%
	Abdominal pain	54	25.70%
	Chest pain /cough	14	6.70%
	Weakness	112	53.30%
	Bleeding episodes	6	2.90%
Hepatic complications	Benign hyperbilirubinemia	67.90%	72
	Acalculous cholecystitis	3.70%	4
	Viral hepatitis	8.40%	9
	Acute hepatic crisis/failure	9.40%	10
	Cholelithiasis	8.40%	9
	Hepatic abscess	1.80%	2
Systemic complications	Renal	6.70%	14
	CNS	1.40%	3
	Musculoskeletal	26.20%	55
	Respiratory	6.20%	13
	Cardiovascular	0.50%	1
	Gastrointenstinal	53.80%	113

	Renal	6.70%	14

The most common chief complaint among the sickled children was pallor (96.2%), followed by weakness (53.3%), jaundice (49%), fever (39%), bone pain (31%), abdominal pain (25.7%), chest pain/cough (6.7%), and bleeding episodes (2.9%). Benign hyperbilirubinemia was the most common hepatic complication (67.9%), followed by acute hepatic crisis/failure (9.4%), viral hepatitis, and cholelithiasis (8.4% each), acalculous cholecystitis (3.7%), and hepatic abscess (1.8%). Gastrointestinal system involvement was predominant (53.8%), followed by musculoskeletal (26.2%), renal (6.7%), respiratory (6.2%), CNS (1.4%), and cardiovascular (0.5%). Significant differences were observed in acalculous cholecystitis, viral hepatitis, acute hepatic crisis, cholelithiasis, and hepatic abscess between SS and AS patients (p value < 0.05). No significant difference was found in mild liver dysfunction or benign hyperbilirubinemia.

The most common ultrasonographic findings were splenomegaly (48.57%), hepatosplenomegaly (37.6%), and hepatic parenchymal disease (17.1%).

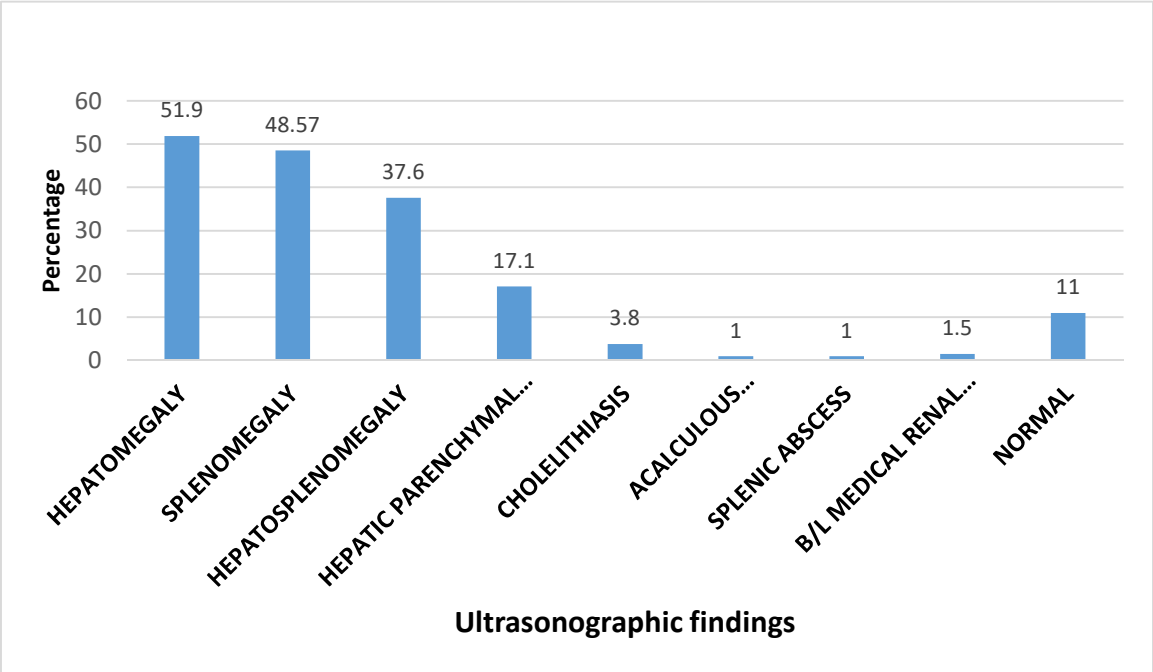

Figure 2: Ultrasonographic Findings Of Study Participants

Significant age-wise differences were observed in benign hyperbilirubinemia, acalculous cholecystitis, and overall prevalence of hepatic complications.

Table 2 : Age Group Distribution Of Various Hepatic Complications

Hepatic complications	1 - 5 yrs	6 - 10 yrs	11-14 yrs	p value
Benign hyperbilirubinemia	14.28%(05)	37.37%(37)	39.47%(30)	0.025
Acalculous cholecystitis	0%(0)	0%(0)	5.26%(04)	0.027
Viral hepatitis	0%(0)	6.06%(6)	3.94%(03)	0.309
Acute hepatic crisis/failure	0%(0)	6.06%(6)	5.26%(04)	0.304

Cholelithiasis	0%(0)	3.03%(3)	7.89%(06)	0.113
Hepatic abscess	0%(0)	0%(0)	2.63%(02)	0.169
Total	14.28%(05)	52.52%(52)	64.47%(49)	0.000

Deaths occurred in 5.7% cases, with a significant difference between SS and AS varieties (p=0.001). Recovery rates did not show significant variation between the two varieties.

Table 3 Outcome Of Sickle Cell Patients				
Outcome	**n=106**	**n=10(AS)**	**n=96(SS)**	**p value**
Death	5.7%	33.33%	66.67%	0.001
Recovery	94.3%	92.3%	95.8%	0.308

Significant differences were observed in several parameters, including Hb, reticulocyte count, HbF, HbS, serum bilirubin, SGPT, PT, DOH, and blood transfusion.

Table 4: Mean Of All Parameters (As Vs Ss)					
PARAMETERS	**MEAN WITH SD**	**AS MEAN WITH SD**	**SS MEAN WITH SD**	**P VALUE**	**SIGNIFICANCE**
Hb	6.72±2.06	8.93±1.75	6.44±1.93	0.002	Y
TLC	12322±5326.66	10156±2893.92	12558±4499	0.166	N
Reticulocyte Count	4.78±3.44	1.91±1.29	5.14±3.46	0.000	Y
HbF	16.29±14.86	3.49±1.11	13.74±10.53	0.000	Y
HbS	68.71±14.15	39.57±8.23	72.30±9.95	0.000	Y
S.Bilirubin(total)	6.18±8.56	4.36±6.58	6.41±8.76	0.000	Y
S.Bilirubin(direct)	2.82±5.00	1.77±2.80	2.92±5.13	0.004	Y
SGPT	118.93±232.17	84.89±116.14	123.11±242.51	0.048	Y
SGOT	103.92±172.55	103.31±156.45	103.98±174.81	0.117	N
ALP	160.65±171.65	132.49±172.42	164.10±171.94	0.050	Y
PT	14.01±2.00	13.62±0.97	14.06±2.28	0.018	Y
INR	1.23±0.35	1.22±0.36	1.23±0.35	0.071	N
DOH	4.91±2.76	3.65±2.23	5.06±2.78	0.006	Y
Blood Transfusion	5.12±5.80	0.39±0.94	5.71±5.88	0.000	Y

The tables provide a snapshot of the demographic, clinical, and laboratory characteristics of sickle cell disease in the studied population, shedding light on age distribution, gender prevalence, chief complaints, hepatic complications, organ system involvement, ultrasonographic findings, age-wise differences in complications, outcomes, and mean values of various parameters.

Discussion

The majority of cases were found in the 6-10 years age group, with cases registered between 1.8 and 14 years. Clinical symptoms were typically absent during the first year of life due to the protective influence of fetal hemoglobins and the relatively small amount of HbS in red blood cells. Fetal hemoglobin tended to suppress the sickling phenomenon (R. B. Scott, 1963). There was minimal difference in incidence between the 6-10 years and 11-14 years age groups, and manifestations became more intense with age (Swarnakar et al., 2003). The age distribution in the second and third groups was similar to previous studies.

The incidence in this study was comparable to Swarnakar et al. (2003), where the male-to-female ratio was 1.08:1. Other studies indicated a higher male preponderance due to more clinical manifestations in males engaging in outdoor activities. The variation in this study may have been explained by the neglect of minor ailments in female children at initial stages, leading to more severe complications and hospital admissions. In the SS variety, characterized by a higher percentage of HbS, there were more crisis episodes, severe anemia, and fever, resulting in increased hospital reporting compared to AS variety. Pallor was a significant presenting complaint due to the shorter lifespan of sickle cells, leading to a chronic hemolytic state. Acute events like hyperhemolytic crisis and sequestration crisis, along with infections and the use of antioxidant drugs, contributed to anemia incidence. Jaundice was common (49%) and associated with increased indirect bilirubin due to excessive hemolysis. Fever (39%) was attributed to infections and tissue necrosis during painful crises, with sickle cell anemia patients being susceptible to various infections. Bone pain/crisis was a common indication for hospitalization.

Abdominal pain (25.7%) was comparable to Praharaj et al. (1969), and bleeding episodes (2.9%) aligned with Konotey-Ahulu (1974) and Paul Heller et al. (1973). 36 Hepatobiliary complications were frequent (50.47%), with a higher incidence in SS variety compared to AS. The study reported varying rates of viral hepatitis, cholelithiasis, and acalculous cholecystitis. Gastrointestinal (53.8%), musculoskeletal (26.2%), and renal (6.7%) complications were observed. The study's cardiovascular complications incidence (0.5%) differed from Ghada OM Ali et al. (2012). Mortality was higher in SS variety (66.67%) than AS (33.3%), aligning with Hamideh et al. (2013).

Mean Hb levels and other parameters were consistent with previous studies. Leucocytosis in SCD was higher than the general population. The analysis of age-wise distribution revealed more complications in older age groups. Days of hospitalization were significantly more in SS groups. The study highlighted the varied complications in sickle cell disease, emphasizing the importance of early detection and comprehensive care.

Conclusion

As individuals age, complications in Sickle Cell Disease (SCD) increase, leading to more frequent hospital reporting due to the absence of HbF's protective influence. A female preponderance (M:F ratio 0.78:1) was noted, and SS variety (89%) outnumbered AS (11%), likely due to fewer hospital admissions for the latter. Complications in SCD, including pallor, weakness, jaundice, fever, bone pain, and abdominal pain, were prevalent. The most common hepatic complication was mild liver dysfunction or benign hyperbilirubinemia, followed by acute hepatic crisis, cholelithiasis, viral hepatitis, and hepatic abscess. The study stressed a multidisciplinary approach for diagnosing and treating multisystemic SCD involvement. Complications were more prevalent in SS than AS groups. Abdominal ultrasound in SCD children revealed high incidences of abnormalities in solid organs. Hepatic complications were more severe in older age groups. Mortality was higher in SS than AS.

In Sickle Cell Anemia (SCA), the majority (67%) had moderate anemia (NNA variety). Baseline Total Leukocyte Count (TLC) exceeded the general population. SGPT/SGOT/ALP were raised in crisis and steady state, with PT/INR deranged in 18% of cases. Blood transfusion needs were higher in SS due to increased chronic hemolysis. Due to the high local prevalence, the study recommended a comprehensive understanding of SCD's incidence. The study concluded that the liver is involved in SCD, displaying clinical features of chronic hemolytic anemia and jaundice. Patients in the locality presenting anemia and jaundice features should be screened for SCD. Increased awareness of hepatobiliary complications, risk reduction,

monitoring, early treatment, and intervention are crucial to decrease mortality.

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