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Study of spectrum of hepatobiliary involvement in children with sickle cell disease

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ABSTRACT

Background: Sickle cell disease (SCD) has various complications among which one of the main organs to be affected is the hepatobiliary system ranging from mild liver function test derangements to significant hepatic abnormalities with marked hyperbilirubinemia. **Aims and Objectives:** We studied the spectrum of hepatobiliary involvement in children with SCD and its association with various factors. **Materials and Methods:** This cross-sectional observational study was conducted at M.Y Hospital Indore, a tertiary centre in central India. All old and new SCD patients under age of 18 years were enrolled sequentially, their detailed history and thorough clinical examination based on a pre-structured proforma noted. Laboratory investigations and radiological evaluation were performed to assess hepatobiliary involvement and its association with various factors was studied. **Results:** Two hundred and two patients with SCD were enrolled during the study period and hepatobiliary involvement was seen in 84 (41.5%) subjects. The most common acute complication was acute hepatic crisis, (20; 9.9%) followed by hepatic sequestration and intrahepatic cholestasis (2; 0.9%). Cholelithiasis was the only chronic complication, seen in 60 (29.7%) patients. Maximum number of patients (53%) were in the age group of 6.1–12 years, least (22%) belonged to 6 months–6 years of age. In our study, 52.5% of patients were females. Symptoms with hepatobiliary involvement were yellowish discoloration of eyes (39.10%), fever (36.10%), abdominal pain (20.8%), vomiting (14.4%), and bleeding (0.9%). Indirect and direct bilirubin, liver enzymes were raised, coagulation profile deranged, and the synthetic function of liver reduced. The most common USG finding was hepatomegaly, seen in 111 (54.9%) patients. Significant association between hepatobiliary involvement with higher HbS concentration, increased frequency of vaso-occlusive crisis/year, and higher transfusion requirement was noted. **Conclusion:** There is significant hepatobiliary involvement in patients with SCD, accounting for great morbidity and mortality requiring high degree of clinical suspicion for timely diagnosis and early treatment.

Key words: Sickle cell disease; Hepatobiliary involvement; Vaso-occlusive crisis

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INTRODUCTION

Sickle cell disease (SCD) affects multiple organ systems, of which one of the main organs to be affected by the disease is the hepatobiliary system. The clinical spectrum of hepatic involvement in SCD ranges from mild liver function test (LFT) abnormalities in asymptomatic patients, to significant hepatic abnormalities with marked hyperbilirubinemia, which can be categorized as acute or chronic. Amongst acute, hepatic crisis, hepatic sequestration, and intrahepatic cholestasis are noted. Cholelithiasis, viral hepatitis, sickle cholangiopathy, and cirrhosis is a few of the chronic complications. These complications are mainly attributed to hemolysis, anemia, requirement of transfusion, repeated sickling, and vaso-occlusion. Preventing infections, timely immunization, adequate nutrition, hydroxyurea, chelation

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therapy, and folic acid supplementation, along with proper hydration, may help reduce the rate of infections, blood transfusions, and hospitalization in these patients, thereby prolonging the onset of hepatobiliary complications.[1]

Patients with SCD have shorter life spans and earlier mortality than other people due to its complications. India has the second-highest SCD burden in the world. Lehman and Cutbush discovered the sickle gene for the 1st time in the Nilgiri Hills tribal population in 1952. Studies conducted in the future have shown that India has a high prevalence of SCD. According to estimates, 3% of India's tribal people have sickle cell anaemia, and another 23% have the sickle cell gene and pass it on to their offspring. Orissa (1–44.4%) has the highest prevalence, followed by Madhya Pradesh (1–40.0%, including Chhattisgarh), Tamil Nadu (1–40.0%), Andhra Pradesh (1–35.7%), and Assam (1–35.5%), Maharashtra (0.8–35.0%), and Gujarat (1–0). Kerala (1–30.0%), Bihar (0.8%; including Jharkhand), Karnataka (1–8.0%), Rajasthan (1–5.7%), West Bengal (1–1.7%), Uttar Pradesh (1.5–18.5%), and Kerala (31.4%).[2]

In Madhya Pradesh, the prevalence of sickle haemoglobin varies by caste and tribal group, from 10% to 33%. It is necessary to map the variations in this gene's prevalence in the various tribal groupings and within a tribal group dispersed across a wide area. Tribals in the state who have normal or sickle hemoglobin make up a sizable component of the Gond and Bhil tribe. While the prevalence rate of sickle hemoglobin varies from 15% to 33% in the Bhils, it ranges from 10% to 25% in the Gonds. India, which has a population of more than 1.2 billion, is expected to be home to more than 50% of the world's SCD patients, and it is estimated that 44,000 infants there, are born with SCA every year. We as a tertiary care health center cater a huge population of SCD children as we lie in the belt of the disease in the region. Early detection of any acute and chronic hepatobiliary dysfunction by monitoring for organ involvement from early years and managing the complications thus become essential. However, the overall research on SCD has been limited in India because it is's a neglected health issue. Thereby increasing the need for such studies in this region.

Aims and objectives

To study the spectrum of Hepatobiliary involvement in children with sickle cell disease and its association with various factors.

MATERIALS AND METHODS

This cross-sectional observational study was carried out at CNBC and M.Y Hospital Indore, a tertiary care center, catering a huge population of SCD patients in the sickle cell belt of Central India. Study was done over a period of 1 year, after obtaining permission from the institution ethics committee. On the basis of prevalence of SCD, the sample size was calculated and a total number of 202 patients of SCD, both newly and pre- diagnosed, by HPLC method, below 18 years of age, attending the OPD and admitted in Pediatric ICU and wards in M.Y hospital, Indore were enrolled sequentially. The subjects having any diagnosed pre-existing chronic liver conditions and those who were on hepatotoxic drugs were excluded. Detailed clinical history and thorough physical examination was noted in a pre-structured pro forma to evaluate for for signs and symptoms of hepatobiliary involvement. Hematological investigations such as CBC, LFT, retic count, Coagulation Profile, Serum ferritin, Hb electrophoresis, HbsAg (IgM HAV titres on case to case basis was done) and radiological investigation (USG abdomen)were done in the patients. Other relevant investigations were done on case to case basis. After proper assessment, they were characterized into acute and chronic complications of hepatobiliary involvement and its association was studied with various factors.Hence, if a patient with SCD presents with acute right upper quadrant pain, nausea, low grade fever, tender hepatomegaly along with hyperbilirubinemia,we thought of acute hepatic crisis. SCD patients presenting with acute hepatic enlargement, pain abdomen, severe pallor, increasing bilirubin along with high retic counts, can be diagnosed with acute hepatic sequestration. We should consider intrahepatic cholestasis, if these patients presents with extreme hyperbilirubinemia, deranged coagulation profile, hepatic failure and thrombocytopenia.

Then, data were entered into Microsoft Excel spreadsheet and analyzed using open sources software. Appropriate tests of significance, like Chi-square test, were applied wherever necessary and $P<0.05$ was considered statistically significant.

RESULTS

In our study, out of 202 patients, the maximum number of patients were in the age group of 6.1–12 years (n=107; 53%) followed by patients in the age group 12.1–18 years (n=51; 25%) and least number of patients belonged to 6 months–6 years of age (n=44; 22%). 106 (52.5%) patients were female compared to 96 (47.5%) that were male, amongst the study subjects.

The most common symptom noted was yellowish discoloration of eyes observed in 79 (39.10%) patients, followed by fever in 73 (36.10%), abdominal pain in 42 (20.80%) vomiting in 29 (14.40%) and bleeding manifestations in 2 patients (0.9%). Pallor was the most

common sign observed seen in 179 (88.60%) patients, followed by icterus in 106 (52.40%), hepatomegaly and splenomegaly in 110 (54.5%) and 113 (55.9%) patients, respectively, hepatic tenderness in 24 (11.8%) and petechiae/purpura, ascites and hepatic failure in 2 (1%) patients each.

Out of 202 enrolled patients of SCD, hepatobiliary involvement was seen in 84 subjects (41.5%), of which the most common acute complication was acute hepatic crisis seen in 20 (9.9%) patients, followed by hepatic sequestration and intrahepatic cholestasis seen in 20 (9.9%) and 2 (0.9%) patients, respectively. Cholelithiasis was the only chronic complication seen in 60 patients (29.7%).

Total bilirubin was raised in all the patients with acute hepatic crisis, intrahepatic cholestasis, and hepatic sequestration and in 58 (96.70%) of patients with cholelithiasis. Direct hyperbilirubinemia was observed in 80% of patients with acute hepatic crisis, 100% patients with intrahepatic cholestasis and 78.3% of patients with Cholelithiasis. Liver enzyme was deranged in patients with intrahepatic cholestasis (100%), acute hepatic crisis (90%), and cholelithiasis (78.3%). Synthetic functions of the liver was affected in 100% patients with Intrahepatic cholestasis, followed by cholelithiasis and acute hepatic crisis. Deranged coagulation profile was observed in all patients with intrahepatic cholestasis, followed by one patient with hepatic sequestration, 10% of patients with acute hepatic crisis and 21.6% of patients with cholelithiasis (Table 1).

The most common finding on the USG abdomen was hepatomegaly, noted in 54.9% patients, followed by cholelithiasis seen in 29.7% and altered liver echotexture, in 14.4% patients.

The correlation of hepatobiliary involvement with multiple factors was studied. With increasing age, its involvement was observed to be higher. Maximum cases were in the age group of 12.1–18 years (58.82%), and the least number of cases were seen in 6 months–6 years of age (34.10%). However, this data was not found to be significant (P=0.78).

Higher HbS levels were associated with increasing hepatobiliary involvement, with maximum involvement in patients with HbS levels >80% (50.00%) and least in those with HbS below 50% (9.5%) patients, with a P=0.03.

Maximum hepatobiliary involvement was seen in patients who had the frequency of vaso-occlusive crisis >6/year (66.6%) and least in those with <4 VOC/year (41.7%), with a P=0.001 (Table 2).

Children who were more frequently transfused had higher Hepatobiliary involvement. It was observed to be maximum in children who received BT every 1–2 months (61.10%) and least in those who received blood transfusions once a year or less (36.5%), with P<0.05.

We also studied the effect of serum ferritin levels on liver enzymes. Derangement of enzymes was noted to be higher with increasing serum ferritin levels such that maximum derangement (100%) was among patients with serum ferritin >5000 ng/mL, followed by 41.6% derangement in those with serum ferritin >1000 ng/mL and least in those with serum ferritin <1000 ng/mL (35.9%). The P=0.007 Serum ferritin levels were not obtained for the remaining 46 patients (Table 3).

DISCUSSION

A total of 202 SCD patients, both pre-diagnosed and newly diagnosed by Hb were recruited in this study. Hepatobiliary involvement was seen in 41.5% of these patients. Majority of these patients were in the age group of 6.1–12 years (53%), followed by the age group of 12.1–18 years (25%) and the least number of patients were under 6 (22%) years. Our results were similar to the study done by Bokade et al.,[3] in Nagpur, where majority of their patients, i.e., 49.23%, also belonged to the age group of 6.1–12 years, followed by 27.18% between 3.1 and 6 years and 23.59% in 6 months and 3 years age group.

Table 1: Laboratory profile of patients with hepatobiliary involvement

Deranged values	Acute hepatic crisis		I/H cholestasis		Cholelithiasis		Hepatic sequestration	
	Number	%	Number	%	Number	%	Number	%
Total bilirubin	20	100	2	100.00	58	96.70	2	100.00
Direct bilirubin	16	80.00	2	100.00	47	78.30	0	0.00
Indirect bilirubin	4	20	2	100.0	37	61.6	2	100.00
SGOT	18	90.00	2	100.00	47	78.30	0	0.00
SGPT	18	90.00	2	100.00	47	78.30	0	0.00
Alkaline phosphatase	8	40.00	0	0.00	29	48.30	0	0.00
Total protein	2	10.00	2	100.00	13	21.70	0	0.00
Serum albumin	2	10.00	2	100.00	8	13.30	0	0.00
Prothrombin time	2	10.00	2	100.00	13	21.60	1	50.00
INR	2	10.00	2	100.00	13	21.60	1	50.00

Almost equal number of males and females (52.5% of females and 47.5% of males) were enrolled in our study.

The most common symptom at presentation was yellowish discoloration of the skin (39.10%), followed by fever seen in 36.10% of patients, abdominal pain in 20.80%, vomiting in 14.40% and 0.9% of patients had some form of bleeding manifestation. Similar to our study, Bokade et al.,[3] in their study observed that yellowish discoloration was the most common presentation of patients, seen in 61.02% of patients, followed by abdominal pain in 37.4% of patients, fever in 28.71%, and vomiting in 23.58%. In another study, Mohanty et al.,[4] studied 60 patients with SCD, and in their study, fever was the most common symptom at presentation seen in 83.3% of patients.

The most common sign observed in the study participants was pallor (88.60%), followed by icterus (52.40%), splenomegaly (55.9%), hepatomegaly (54.5%), hepatic tenderness (11.8%), petechiae/purpura, ascites and signs of hepatic failure (1%).

Hepatobiliary involvement categorized into an acute and chronic complications. Among acute complications, acute hepatic crisis was the most common presentation seen in 9.9% of patients, followed by hepatic sequestration and sickle intrahepatic cholestasis seen in 0.9% of patients. Cholelithiasis was the only chronic complication observed and was seen in 29.7% of patients. Hepatitis B antigen status was negative in all these patients.

Similar results were observed in studies done by Botezelli et al.,[5] and Bokade et al.,[3] where hepatobiliary involvement was observed in 47% and 44% of the patients, respectively. The spectrum of hepatobiliary involvement, as studied by Bokade et al.,[3] was such that, Acute hepatic crisis was found in only in 1.17% of patients, hepatic sequestration in 2.35%, cirrhosis in 4.71%, cholelithiasis in 28.24%, cholecystitis in 27.06%, and viral hepatitis in 36.47% of patients. This is in contrary to Traina et al.,[6] and Koskinos et al.,[7] who reported hepatobiliary involvement in 96% and 39%, respectively, but the latter has been done in adults. In another study of 299 patients of SCD by Curro et al.,[8] 2017 the acute hepatic crisis was seen in 10% of the study population.

The liver function profile of these patients was studied and it was observed that in patients with acute hepatic crisis, total bilirubin was raised in 100% with a predominance of direct component, raised in 80% along with derangement of SGOT/SGPT levels in 90% of them and higher ALP in 40%. Of these patients, 10% had both low total protein and serum albumin levels and a deranged coagulation profile.

In patients with intrahepatic cholestasis, total bilirubin along with the direct and indirect components was raised in all the patients (100%) with deranged liver enzymes and low serum total protein and albumin levels. Deranged coagulation profile along with thrombocytopenia was noted in these patients. All patients (100%) with hepatic sequestration had elevated total and indirect bilirubin levels, severe anemia and increased retic counts and 50% had deranged coagulation profiles.

Total bilirubin was seen to be significantly increased in 96.70% of patients with cholelithiasis, among which 78.30% had high direct bilirubin levels, along with raised indirect bilirubin in 61.6% of patients. SGOT/SGPT levels were deranged in 78.3% of patients, along with high ALP levels in 48.3% of these patients and hypoproteinemia and hypoalbuminemia in 21.7% and 13.3%, respectively. About 21.6% of these patients had a deranged coagulation profile. Bokade et al.,[3] in their study shows that direct bilirubin was high in all the subjects with cholilithiasis and 91.3% among patients with cholecystitis, indirect bilirubin was raised in

Table 2: Association of hepatobiliary involvement with various factors

Factors	Hepatobiliary involvement		
	Count	Percent	P-value
HbS concentration			
<50 (21)	2	9.5	0.03 Significant
50–80 (103)	46	44.7	
>80 (72)	36	50	
Frequency of VOC/year			
<4 (104)	43	41.70	
4–6 (40)	23	58.40	0.001
>6/year (33)	18	66.60	Significant
Frequency of blood transfusion			<0.05
Every 1–2 m (36)	22	61.10	Significant
Every 3–6 m (66)	38	57.5	
Every 7–12 m (12)	5	41.60	
Once in 12 m or more (52)	19	36.50	

Table 3: Association of liver enzymes with serum ferritin levels

Ferritin level (ng/mL)	Deranged SGOT		Deranged SGPT		P-value
	Number	Percent	Number	Percent	
<1000 (65)	23	35.90	23	35.90	0.007 Significant
1000–5000 (89)	37	41.6	37	41.6	
5001–10000 (5)	5	100.00	5	100.00	
>10000 (3)	3	100.00	3	100.00	

all the patients having cholecystitis and viral hepatitis and in 87.5% patients with cholelithiasis. ALT was elevated in 93.54% patients with viral hepatitis and ALP was raised in all their subjects who had some form of hepatobiliary involvement.

Hence, if a patient with SCD presents with acute right upper quadrant pain, nausea, low grade fever, tender hepatomegaly along with hyperbilirubinemia, we should think of acute hepatic crisis. SCD patients presenting with acute hepatic enlargement, pain abdomen, severe pallor, increasing bilirubin along with high retic counts, can be diagnosed as acute hepatic sequestration. We should consider intrahepatic cholestasis, if these patients present with extreme hyperbilirubinemia, deranged coagulation profile, hepatic failure, and thrombocytopenia.

Such a laboratory profile can be explained by the recurrent vasoocclusive crisis, the regular blood transfusions, amongst other reasons that ultimately affect the liver functions, namely the synthetic functions and also cause cytotoxic injury to the liver cells resulting in deranged enzyme levels.

Ultrasound abdomen was performed in all the patients with SCD and hepatomegaly was noted in 54.9% of these patients, altered liver echo texture was observed in 14.4%% and 29.70% patients had cholelithiasis. According to the study done by Bokade et al.,[3] hepatomegaly was noted in 76.47% patients, liver parenchymal disease in 36.47%, cholelithiasis in 29.4%, cholecystitis in 27.05%, cirrhosis in 4.7% and hepatic infarct in 1.1% of patients. Jacquemin et al., (2021) also quoted that cholelithiasis is quite frequent in patients with HbSS.[9]

Hepatobiliary involvement was maximum i.e., 58.82% in children 12.1–18 years, and minimum among younger patients belonging to 6 months–6 years of age i.e., 34.10% with a P=0.78. Bokade et al.,[3] also concluded in his study that overall, the hepatobiliary involvement was seen to be more as age of the patients increased.

Patients with HbS levels of >80% were observed to have maximum hepatobiliary involvement that was noted in 50.0%, followed by 44.7% of patients who had HbS levels between 50 and 80% and 9.5% of patients who had HbS <50%. This data were found to be statistically significant such that liver involvement increased with increasing HbS levels (P=0.03).

Hepatobiliary Involvement was maximum amongst those with VOC episodes of >6 per year, (66.6%), followed by 58.4% involvement in patients who had VOC episodes of 4–6/year and 41.7% involvement in those with VOC <4/year, with P=0.001. This increase in HBI with increasing VOC/year can be attributed to recurrent ischemic injuries to the liver.

The association of hepatobiliary involvement with frequency of blood transfusion demonstrated that higher involvement was seen in patients who were frequently transfused. Maximum hepatobiliary involvement was seen in patients who needed blood transfusions every 1–2 months (61.1%), followed by those who received blood transfusions every 3–6 m (57.5%). Of patients, who received blood transfusion every 7–12 months and those who received blood once every year, 41.6% and 36.5% of patients showed features of hepatobiliary involvement, respectively. This was a significant association with a P<0.05. These findings are consistent with the study by Qhalib and Zain who found in his study that hepatobiliary complications were significantly higher in those patients, who were frequently admitted to the hospital and/or had frequent blood transfusions.[10]

We also studied the effect of serum ferritin levels on the liver enzymes and it was observed that SGOT and SGPT was deranged in 100% of patients who had their ferritin >5000, 41.6% of patients who had serum ferritin levels >1000 and 35.9% in those with serum ferritin levels of <1000 ng/mL. This association of deranged liver enzymes with increasing serum ferritin levels was statistically significant (P=0.007). Various studies have suggested that persistently high ferritin levels, although they may also be elevated in inflammatory processes and some chronic diseases, may correlate with the number of transfusions and hepatic iron deposits.

Limitations of the study

- T2* MRI Scan which is the method of choice for detecting and quantifying hepatic iron load was not done in patients with high serum ferritin levels,due to lack of resources.
- Work up to rule out primary liver pathology like liver biopsy was not done.

CONCLUSION

Hepatobiliary involvement was found in 41.5% of the study participants with SCD. Most common acute and chronic complications being acute hepatic crisis and cholelithiasis, respectively. It is a fairly common complication in these children due to recurrent VOCs, regular blood transfusions, and hospitalizations and brings about significant morbidity in these patients. Through this study, we have tried to highlight the various hepatobiliary complications that can manifest in these children, with their clinical features and lab parameters, for their early detection, essential in reducing the morbidity and mortality in these patients

of SCD. This study can be expected to fill the lacunae that exists regarding hepatobiliary involvement in these children.

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REFERENCES

1. Kleigman RM, St Geme JW, Blum NJ, Shah SS and Tasker RC. Wilson Nelson Textbook of Pediatrics. 21st ed. Netherlands: Elsevier; 2019.
2. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease--life expectancy and risk factors for early death. N Engl J Med. 1994;330(23): 1639-144.
   https://doi.org/10.1056/NEJM199406093302303
3. Bokade CM, Chauhan U and Dhole C. Study of hepatobiliary involvement in children with sickle cell disease. Ann Int Med Dent Res. 2017;3(3):P9-P15.
4. Mohanty AP, Yellapu V, Kumar KM, Saxena A and Deo DS. A study of hepatobiliary involvement in adult patients with sickle cell disease. Int J Adv Med. 2020;7(9):1361-1366.
5. Botezelli JD, Cambri LT, Ghezzi AC, Dalia RA, Voltarelli FA and de Mello MA. Fructose-rich diet leads to reduced aerobic capacity and to liver injury in rats. Lipids Health Dis. 2012;11:78.
   https://doi.org/10.1186/1476-511X-11-78
6. Traina F, Jorge SG, Yamanaka A, de Meirelles LR, Costa FF and Saad ST. Chronic liver abnormalities in sickle cell disease: A clinicopathological study in 70 living patients. Acta Haematol. 2007;118(3):129-135.
   https://doi.org/10.1159/000107744
7. Koskinos J, Manesis EK, Zacharakis GH, Galiatsatos N, Sevastos N and Archimandritis AJ. Liver involvement in an acute vaso-occlusive crisis of sickle cell disease: Prevalence and predisposing factors. Scand J Gastroenterol. 2007;42(4): 499-507.
   https://doi.org/10.1080/00365520600988212
8. Curro G, Meo A, Ippolito D, Pusiol A and Cucinetta E. Asymptomatic cholelithiasis in children with sickle cell disease, early or delayed cholecystectomy? Ann Surg. 2017;245(1):126-129.
   https://doi.org/10.1097/01.sla.0000242716.66878.23
9. Jacquemin E, de Vree JM, Cresteil D, Sokal EM, Sturm E, Dumont M, et al. The wide spectrum of Multidrug Resistance 3 deficiency: From neonatal cholestasis to cirrhosis of adulthood. Gastroenterology. 2021;120(6):1448-1458.
   https://doi.org/10.1053/gast.2001.23984
10. Qhalib HA and Zain GH. Hepatobiliary complications of sickle cell disease among children admitted to Al Wahda teaching hospital, Aden, Yemen. Sultan Qaboos Univ Med J. 2014;14(4):e556-e560.

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AD- Literature survey, Prepared first draft of manuscript implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article. **PM**- Concept, Design of study, clinical protocol,statistical Analysis and Interpretation. Review Manuscript. **UC**- Concept, literature survey, manuscript preparation, editing, and manuscript revision.

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