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Original Research Article

A study of hepatobiliary involvement in adult patients with sickle cell disease

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ABSTRACT

Background: Sickle cell disease (SCD) encompasses a group of hemoglobinopathies characterized by a single amino acid substitution in the ß-globin chain. Hepatobiliary complications are frequent among sickle cell disease patients. Sickle cell disease has been extensively studied. However, data about hepatobiliary abnormalities among the adult age group are limited. Aim of our study aims to find the prevalence of hepatic-biliary involvement in Sickle cell disease in adult patients admitted to our hospital.
Methods: A prospective study was done for a period of two years from October 2017 to October 2019. Subjects of both sexes above the age of 18 years with SCD admitted to our hospital were enrolled. Thorough history taking, full clinical examination, hematological and biochemical parameters assessment, and abdominal ultrasonographic studies were performed to all patients.
Results: The results obtained showed that 59% of patients had hepatobiliary involvement. The most common symptom among these patients was bone pain, and the pallor was the most common sign. Biochemical tests revealed reduced hemoglobin concentration, elevated bilirubin, and compromised liver function. The most common ultrasound finding in this study was hepatomegaly, hepatosplenomegaly, cholelithiasis, and gall bladder sludge. The incidence of viral hepatitis was low compared to previous studies. Other hepatobiliary complications were cholelithiasis (14%), benign hyperbilirubinemia (14%), cholecystitis (8%) hepatic crisis (9%), hepatic sequestration (1%) , liver cirrhosis (1%), choledocholithiasis (1%) and cholangitis (1%).
Conclusions: Hepatobiliary complications, particularly gallbladder diseases, are frequent among SCD patients. The early detection of hepatobiliary complications by repeated ultrasound screening and liver function tests is significant as their frequency and intensity are related to the patient's age and the duration.

Keywords: Adult patients, Hepatobiliary involvement, Sickle cell disease

INTRODUCTION

Sickle cell disease (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.[1] Sickle cell disease is a multisystem disorder and can affect any part of the body. One of the main organ to be affected is hepatobiliary system.[2] The hepatobiliary complications are due to hemolysis, the

problems of anemia, transfusion management, the consequences of sickling, and vaso-occlusion. Biliary involvement is common in SCD patients. Cholelithiasis is one of the most frequently encountered biliary complications of SCD.

Besides cholelithiasis, choledocholithiasis, cholecystitis, cholangitis, and sickle cell cholangiopathy are some of the other biliary manifestations seen in sickle cell disease patients. These complications of the sickling disorders are most common in Sickle cell disease (HbSS) than a sickle trait. Early detection of biliary manifestations is essential in reducing the morbidity and mortality in SCD. In patients of sickle cell disease, there are repeated attacks of jaundice, hepatic infarction, acute and chronic hepatitis, and cirrhosis.[3] There are several possible mechanisms of hepatic involvement, which are as sickled cells in sinusoids are causing sinusoidal obstruction and anoxic necrosis of hepatic cells; sickled cells in the hepatic artery are causing hepatic infarcts and focal necrosis; chronic hemolysis with accelerated bilirubin turnover causing cholelithiasis, choledocholithiasis, and cholestasis; factors associated with primary disease but related to transfusion therapy, like a transfusion Iron overload, hemosiderosis, and viral hepatitis.

The term "sickle cell hepatopathy" is sometimes used to reflect the overlapping causes of liver dysfunction in these patients. It's spectrum ranges from mild hyperbilirubinemia to fulminant hepatic failure. Various manifestations include hepatic crisis, hepatic sequestration, intrahepatic cholestasis, viral hepatitis, cirrhosis, chronic liver disease, and overt liver failure. Early detection of hepatic dysfunction is essential in reducing the morbidity and mortality in SCD.[4] Sickle cell hemoglobinopathy is common in Western Odisha.[5] A significant number of these patients have hepatobiliary manifestations. There have been some published studies on hepatobiliary manifestation in children and only a few studies in adult patients with SCD. This work was undertaken to investigate the frequency and pattern of hepatobiliary manifestations in hospitalized adult patients in our centre, a tertiary care hospital in Western Odisha.

Aim and objectives of the study were to find the prevalence of hepatobiliary involvement in Sickle cell disease in adult subjects admitted to our hospital. Also, to investigate the frequency and pattern of hepatobiliary manifestations in hospitalized adult patients in our centre, which is a tertiary care hospital in Western Odisha.

METHODS

This prospective study was conducted on patients of sickle cell disease of both sexes aged 18 years or above. They were admitted to the medicine wards of Kalinga Institute of Medical Sciences and PBM Hospital, Bhubaneswar, Odisha, during that period from October 2017 to October 2019, who fulfilled the inclusion and exclusion criteria. Permission of the Hospital ethics committee was obtained before the commencement of the study.

Inclusion criteria

Inclusion criteria were patients admitted with a diagnosis of sickle cell disease which is based upon Hb Electrophoresis by HPLC (high-performance liquid chromatography); the patient's age of 18 years and above and the patients who gave consent.

Exclusion criteria

Subjects with combined hemoglobinopathies, subjects with congenital hepatic malformations, those who are not willing to give consent, pregnancy and the patients who were hospitalized in a critical state were excluded.

Methodology

The nature of the study was explained to all participants and written informed consent obtained from them. Detailed history with particular emphasis on hepatobiliary disease, past history of a number of episodes of vaso-occlusive crises, frequency, and a number of blood transfusions during previous hospitalizations was elicited.

History of drug use was obtained for each patient, including both licit drugs, alcohol, and hepatotoxic drugs, such as antitubercular drugs, phenothiazines. All the cases were subjected to detail general physical examination, as mentioned in the proforma.

Patients were evaluated based on symptoms at the time of admission and hospital stay, clinical findings, laboratory investigations, CBC and peripheral smear, LFTs, sickling test (Daland and Castle method), Hb Electrophoresis (HPLC), USS of liver and biliary system, complications associated, if any treatment, outcome.

Statistical analysis

All data were collected, organized in a tabulated form, and statistically analyzed. All statistical calculations were done using SPSS (Statistical Package for the Social Science (SPSS Inc., Chicago) version 16 and Microsoft Excel version 7 (Microsoft Corporation, New York). Descriptive data for continuous variables were presented as median [IQR], mean±SD, and range. Categorical variables were presented as frequencies and percentages.

RESULTS

In the current study, the median age of the patients was 27 years with interquartile range (IQR) 18-60. Females represented 45% (n=100) of the total sample. The majority of the patients presented with bone pain (66%). Chest pain was present in 36 (36%) patients. Yellowish discoloration of eyes and urine was present in 33 patients

(33%), fever, and right upper quadrant abdominal pain in 24% and 21% of patients, respectively. The analysis of signs in study subjects revealed that pallor was the most common sign and present in 72 patients (72%) followed by icterus in 47 patients (47%), hepatomegaly in 27 patients (27%) and liver tenderness in 19 patients (19%).

Sickling test was done in all patients, and it is positive in all the patients, and subsequently, HPLC was done results shown in 9 (Table 1). The hematological tests revealed reduced hemoglobin with a mean value of 8.522±2. Total Leucocyte Count (TLC) was either increased or decreased in most on patients reflecting infection is the most common insult with mean value of10.146±5.3. In most of these patients, platelet count was normal (Table 1).

Table 1: Laboratory characteristics of SCD patients.

Variables	Mean±SD	Median (IQR)
Hb (g/dl)	8.522±2.31	8.65 (2.58-13.42)
WBC (10^3/ml)	10.146±5.3	9.18 (2.5-24.6)
Platelets (10^3/ml)	208.7±126.1	156.5 (34.9-611)
Reticulocytes (%)	5.53±5.3	3.9 (0.5-18)
Total bilirubin (mg/dl)	4.78±7.86	2.1 (0.16-42.3)
Direct bilirubin (mg/dl)	3±6.33	0.59 (0.07-32.68)
ALP(U/L)	147.2±139.2	105 (44-1170)
GGT(U/L)	47.86±39.46	34.86 (4.9-200.8)
ALT(U/L)	192.51±538.2	39 (8-3579)
AST(U/L)	266.92±883.9	46 (6-8366)
PT(SEC)	14.2±3.8	13 (11.1-27.2)
HbS (%)	68.5±15.3	69.1 (51.8-74.4)
HbF (%)	13.3±13.9	12.4 (0–18.2)

WBC: White blood cells; Hb: Hemoglobin;AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Glutamyl gamma transferase; ALP: Alkaline phosphatase

Liver function tests (LFTs) were done in all patients. In 60%, serum bilirubin was elevated (Table 2) with a mean value of 4.78±7.86 and interquartile range (IQR) 0.16-42.3. Serum alkaline phosphatase (ALP) was elevated in 35%. Reduced serum total protein is found in 11% and reduced serum albumin in 22 %. Elevated alanine aminotransferases (ALT) was found in 40 patients with a mean value of 192.51±538.2, IQR of 8-3579 and elevated aspartate aminotransferase (AST) was found in 52 patients mean value of 266.92±883.9, IQR of 6-8366 and elevated gamma-glutamyl transferase (GGT) was found in 22 % of patients. Ultrasonographically detected abnormalities among our study group were shown in (Table 3).

Hepatomegaly was the most common finding seen in 37 % of patients; gall bladder sludge was found in 10% and calculi in 15% patients, respectively.

Table 2: Abnormal laboratory results detected among the study group in LFT.

Variables	Frequency	Percentage
Elevated serum total bilirubin	60	60
Elevated serum direct bilirubin	40	40
Elevated serum ALP	35	35
Reduced serum total proteins	11	11
Reduced serum albumin	22	22
Serum ALT level		
One fold rise	24	24
Two fold rise	5	5
Three fold rise	11	11
Serum AST level		
One fold rise	24	24
Two fold rise	6	6
Three fold rise	22	22
Serum GGT level		
One fold rise	15	15
Two fold rise	6	6
Three fold rise	1	1

Table 3: Findings elicited by ultrasonography among SCD patient.

Variables	Sonographic finding	Frequency	Percentage
Hepatomegaly	-	37	37
Liver Echogenicity	Normal	93	93
	Distorted	7	7
	Heterogenous pattern	5	5
	Isolated coarse hepatic echotexture	2	2
	Coarse echotexture with nodular surface and portal vein changes	1	1
Intrahepatic biliary duct	Normal	99	99
	Abnormal	1	1
Portal vein	Normal	99	99
	Dilated	1	1
Common bile duct	Normal	99	99
	Dilated	1	1

Continued.

Variables	Sonographic finding	Frequency	Percentage
Gall bladder	Contracted	4	4
	Distended	3	3
	GB Sludge	10	10
	Single calculi	1	11
	Multiple calculi	14	14
Other features	GB Polyp	1	1
Spleen	Splenomegaly	34	34
Autosplenctomy	Spleen not visualized	6	6

Table 4: Hepatobiliary complications encountered among the study group.

Variable	Frequency	Percentage
Hepatic crisis	9	9
Hepatic sequestration	2	2
Benign hyperbilirubinemia	13	13
Acute hepatitis	6	6
Liver cirrhosis	1	1
Chronic liver disease	1	1
NAFLD	5	5
Cholelithiasis	14	14
Cholecystitis	8	8
Cholangitis	1	1
Choledocholithiasis	1	1
Gall bladder sludge	10	10
Gall bladder polyp	1	1

Table 5: Procedures performed.

Procedures	Number
ERCP and stenting (choledocholithiasis)	1
Laparoscopic cholecystectomy (symptomatic cholelithiasis)	4
open cholecystectomy (symptomatic cholelithiasis)	1

In our study, hepatobiliary involvement was seen in 59% of patients. Among 59% of patients who had hepatobiliary involvement, primarily biliary system was involved. Cholelithiasis was found in 14% of patients, cholecystitis was found in 8% patients. Gall bladder mud was found in 10% of patients. Choledocholithiasis, cholangitis, and gall bladder polyp was found in each patient each. In the liver, the hepatic crisis was found in 9% patients, hepatic sequestration was found in 2% of patients. Benign hyperbilirubinemia was found in 13% of patients. Acute viral hepatitis was found in 6 patients. Nonalcoholic fatty liver disease (NAFLD) was found in 5% patients. One patient was found to have cirrhosis, and one patient was diagnosed with chronic liver disease (Table 4).

In one patient who had choledocholithiasis Endoscopic retrograde cholangiopancreatography (ERCP) and stenting was done successfully. Laparoscopic and open cholecystectomy was done in 4 and 1 patients, respectively, for symptomatic cholelithiasis patients (Table 5).

DISCUSSION

In our study, bone pain was present in 66% of patients; fever was present in 40%, yellowish discoloration of urine and eyes in 33%, and right abdominal pain in 21% patients. The study done by Bokade, fever was found in 28.71% of patients, yellowish discoloration of urine and eyes in 61%, and right abdominal pain in 37.4%.[6] In Johnson et al study, bone pain was present in 72% of patients and fever in 34%.[7] In the Mahebba study, bone pain was present in 100% of patients and abdominal pain in 1 % of patients.[8] So, the most common presentation was bone pain and fever.

The most common sign in our study was pallor found in 72 % of patients. In the study by Pallor B was present in 89.23% patients, and in Mahebba study, pallor was found in 70% of patients. Dalia et al study pallor was found in 84 %, and in the sarkar[10] study, it was 70%.[9] In our study, jaundice was seen in 47% of patients. In agreement with Dal and Coworkers detected jaundice in 52.9% of their SCD study group, but Almeida detected jaundice in 60% of their SCD study group.[11] In the Bokade study, jaundice was found in 45%, and in the Johnson et al study, it was found in 62%. In our study, the mean value of hemoglobin was 8.522 gm/dl, and in Mahebba, it was 9.3gm/dl. In Dalia et al study, the mean value of

hemoglobin was 8.3 gm/dl. The patients had increased bilirubin and albumin levels and WBC count, as had been established in the earlier studies like Ebert and Curtis study.[12-14] In our study group, 40% of our patients had a two to three-fold rise in ALT level, while 42% had three folds rise in serum AST levels. Contradictory to this, Dalia et al. found elevated AST in 7 patients and ALT in 6 patients, but Almeida's study reported higher elevations in serum AST levels in 47.8% of their study group. In contrast, serum ALT levels were high in 14.2%. Among our study group, total bilirubin levels were elevated in 60%, while direct bilirubin levels were above the normal range in 40% of the cases. GGT was found to be elevated in about 22 % of patients. In Dalia et al study, serum total bilirubin was elevated in 42% patients and direct bilirubin in 50 % of patients.

In our study, only 21 of the 100 performed ultrasounds were normal, similar to study by Mohanty et al ultrasound was normal in 20 % of patients.[15] Hepatomegaly was found in 37% of patients similar to Dalia and Almeida, who found hepatomegaly in 34.3% and 30.4% subjects respectively, but Oparinde et al and Papadaki found hepatomegaly in 70% of patients.[16,17] Splenomegaly was the common sonographic feature of the spleen in our study found in 34% of patients similar to previous studies like Eze and Lozano.[18,19] In our study gall stones were detected in (14%), which is lower than some studies like Gumiero et al in which gall stones were detected in 45% but similar to studies like Mc Carville et al and Bokade in which gall stones were found in 21% and 29% respectively.[20,21] In our study, there were 10 % of patients who had gall bladder sludge, which is similar to studies by Mahebba (12 %) and Dalia (14 %).

In this study hepatobiliary involvement was seen in 59% of patients contrary to Traina et al and Koskinas et al reported hepatobiliary involvement in 96% and 39% respectively but similar to Sarkar (63%), Dalia et al (47%) and Bokade (44%) but the latter two studies were done in children.[22,23] In 9% of patients in our study, the acute hepatic crisis was diagnosed, which was similar to study done by Ebert et al (10%) and 9% by Sarkar, but on the contrary, it was found only in 2% by Dalia and 1% by Bokade. In our study, 2% of patients had a hepatic sequestration crisis similar to the studies of Bokade et al, where hepatic sequestration was found in 2 % patients, but in studies done by Dalia et al and Mahebba et al no patient was diagnosed with hepatic sequestration crisis. In our study, we did not find any patient with acute sickle cell intrahepatic cholestasis, which is a fatal condition. Fortunately, it is very rare with a total of only 17 reported cases so far in Khan M study.[24]

In our study, six patients were diagnosed to have acute viral hepatitis. In these, six patients had acute HAV hepatitis and HEV hepatitis in 1 patient. We did not see any HBV or HCV in our cases. This could be due to universal immunization against HBV, screening for HBV and HCV at blood banks before blood transfusion. Both Torres et al and Hassan et al reported that the Anti-HCV antibody in 14.1% and 10.1%, respectively.[25,26] However, in a study done by Ocak et al on 339 patients of SCD, only 0.75% of their patients were HCV seropositive.[27] In our study, we found one patient had cirrhosis similar to the work by Dal and Bokade, but Ebert encountered liver cirrhosis in 7.6% of their study group. There are Isolated case reports to small case series like Green and Klion reporting acute liver failure in SCD.[28,29] However, we did not encounter any case in our study. In our study, there were eight patients diagnosed with cholecystitis. Gumero et al found cholecystitis in 10% of patients and Bokade in 21% of patients.

CONCLUSION

In conclusion, the hepatobiliary involvement of sickle cell disease in younger adults is not rare. The common symptoms are fever, bone pain, right upper abdomen, and yellow discoloration of eyes. The clinical spectrum of hepatobiliary involvement in sickle cell disease ranges from jaundice, hepatomegaly, splenomegaly, acute sickle cell crises, hepatic sequestration crises, cholelithiasis, choledocholithiasis, biliary sludge, and cholecystitis. Acute or chronic intrahepatic cholestasis, overt liver failure, autoimmune hepatitis, or sickle cell cholangiopathy are rare. Viral hepatitis with HBV, HCV, is rare. Liver function tests and Ultrasound examination of the hepatobiliary tract are two most essential investigations in classifying various types of hepatobiliary involvement.

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