Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Study of Hepatobiliary Involvement in Children with Sickle Cell Disease.

C. M. Bokade[1], Urmila Chauhan[2], Charushila Dhole[3]

[1]Professor and Head, Department of Pediatrics, GMCH, Nagpur.
[2]Associate Professor, Department of Pediatrics, GMCH, Nagpur.
[3]Assistant Professor, Department of Paediatrics, GMCH, Nagpur.

Received: March 2017
Accepted: March 2017

ABSTRACT

Background: Sickle cell disease (SCD) encompasses a group of haemoglobinopathies characterized by a single amino acid substitution in the ß-globin chain. Sickle cell disease is a multisystem disorder can affect any part of the body .One of the main organ to be affected is hepatobiliary system.[1] The liver can be affected by a number of complications due to the disease itself and its treatment. The clinical spectrum of hepatic involvement in SCD ranges from mild liver function test abnormalities in asymptomatic patients, to significant hepatic abnormalities with marked hyperbilirubinemia. Early detection of hepatobiliary dysfunction is essential in reducing the morbidity and mortality in SCD. **Methods:** 195 Subjects of either sex of age group between 6 month -12 years with sickle cell disease SS pattern were enrolled. Detailed clinical history and subject's data for hepatobiliary involvement by clinical, biochemical and radiological parameters were recorded. Subjects with Hepatobiliary involvement were further defined upon clinical features, Laboratory investigations and Radiological investigations as Viral hepatitis, Cholecystitis, Cholelithiasis, Hepatic sequestration, Acute hepatic crisis **Results:** Hepatobiliary involvement was present in 85 subjects and included viral hepatitis (36.47%), cholelithiasis (28.24%), cholecystitis (27.06%) and cirrhosis (4.71%). All the laboratory parameters- indirect and direct bilirubin, liver enzymes were raised in subjects with hepatobiliary involvement. Most common ultrasonographic finding was hepatomegaly (76.47%), followed by liver parenchymal disease (36.47%) and 4 subjects (4.7%) had cirrhosis. **Conclusion:** Hepatobiliary involvement is common complication in children with SCA requiring frequent blood transfusions, hospitalizations and having increased number of crisis rate. Monitoring for organ involvement from early years and management of complications may reduce long term morbidity and mortality in patients with SCD.

Keywords: Sickle cell anemia, Hepatobiliary involvement, crisis rate.

INTRODUCTION

Sickle cell disease (SCD) is a common genetic disorder. It is characterized by chronic haemolytic anaemia 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 can affect any part of the body .One of the main organ to be affected is hepatobiliary system.[2] Liver and biliary tract abnormalities are common in sickle cell disorder. The liver can be affected by a number of complications due to the disease itself and its treatment.[1] In patients of sickle cell disease, there are repeated attacks of jaundice, hepatic infarction, cholelithiasis, choledocholithiasis, acute and chronic hepatitis and cirrhosis.[3] The hepatobiliary complications are due to haemolysis, the problems of anaemia, transfusion management, the consequences of sickling, vaso-occlusion. These complications of the sickling disorders are most common in sickle cell anaemia (Hb SS) than sickle trait. [3] The term "sickle cell hepatopathy" has sometimes been used to reflect the overlapping causes of liver dysfunction in these patients. Early detection of hepatobiliary dysfunction is essential in reducing the morbidity and mortality in SCD.

Name & Address of Corresponding Author
Dr Urmila Chauhan
Flat no 101, Arya Apartment,
Shrinath Sai Nagar,
Nagpur, 440027.

MATERIALS AND METHODS

The study was done at tertiary care hospital in Nagpur over the period of 2 years. Institutional ethics committee permission was obtained before commencement of the study. Subjects of either sex between age group of 6 month -12 years with sickle cell disease SS pattern reporting to hospital were enrolled. Exclusion criteria were subjects with combined haemoglobinopathies, subjects who do not have confirmed HPLC report, subjects less than 6 month and more than 12 years of age, subjects with previous hepatic involvement, congenital hepatic malformations, patients whose parents were not

willing to give consent. Detailed clinical history was recorded regarding symptoms related to hepatobiliary disease, past history of number of episodes of vaso-occlusive crises, frequency of blood transfusion and hospitalization was recorded. Subject's data for hepatobiliary involvement by clinical, biochemical and radiological parameters were recorded. Data collection of all study subjects was done in structured data collection forms. Detailed Laboratory data was recorded such as Complete blood count, Serum Ferritin, Complete Liver function test profile (ALT, AST, ALP), Total Protein (S. Albumin, Globulin), S. Bilirubin, Coagulation Profile (PT, PTTK, INR), Radiological data records included Ultrasonography of abdomen to assess liver size, gall bladder wall thickening, cholelithiasis and ascites. Subjects with Hepatobiliary involvement were further defined upon clinical features, Laboratory investigations and Radiological investigations as Viral hepatitis, Cholecystitis, Cholelithiasis, Hepatic sequestration, Acute hepatic crisis.

RESULTS

As depicted in Figure 1, majority of the subjects 96 (49.23%) were from the age group 6.1-12 years and 53 (27.18%), 46(23.59%)subjects each from age group of 3.1-6 years, 6 month-3years respectively.

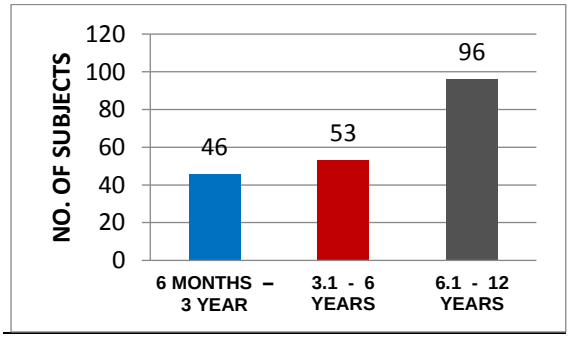

Figure 1: Age distribution in study subjects.

Table 1: Clinical Profile of Study Subjects.

Symptoms	Number(n=195)	Percentage
Fever	56	28.71
Yellowish discoloration of eyes	119	61.02
Ruq abdominal pain	73	37.4
Nausea,vomiting	46	23.58
Signs	**Number(n=195)**	**Percentage**
Pallor	174	89.23
Icterus	125	64.10
Hepatomegaly	109	55.89
Splenomegaly	132	67.69
Hepatic tenderness	63	32.3
Petechiae	7	4.1
Edema	7	3.5
Ascites	7	3.5
Hepatic failure	7	3.5

This table shows clinical profile of subjects. Yellowish discoloration of eyes (61.02%) and right upper quadrant abdominal pain (37.4%) were more common symptoms as compared to fever (28.71%) and nausea and vomiting (23.46%).

In our study, pallor was most common sign (89.23%) followed by splenomegaly (67.69%), icterus (64.10%), hepatomegaly (55.89%), hepatic tenderness 63 (32%) and petechiae, edema, ascites, hepatic failure in each of 7(3.5%) subjects.

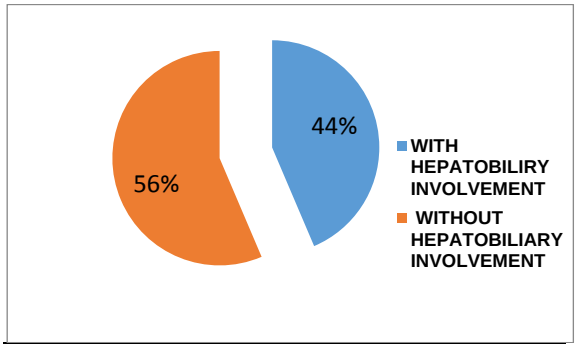

Figure 2: Subjects with and without hepatobiliary involvement.

Figure 2 shows hepatobiliary involvement in subjects. In our study, out of total 195 subjects, 85(43.58%) subjects had hepatobiliary involvement and 110(56.42%) subjects were without hepatobiliary involvement.

Table 2: spectrum of hepatobilliary involvement

Clinical spectrum		Number	Percentage
Viral hepatitis		31	36.47
Cholelithiasis		24	28.24
Cholecystitis		23	27.06
Others	Cirrhosis	4	4.71
	Hepatic sequestration	2	2.35
	Acute hepatic crisis	1	1.17
Total		85	100

Table 2 shows spectrum of hepatobiliary involvement. In our study, out of 85 subjects with hepatobiliary involvement, 31(36.47%) subjects had viral hepatitis, 24 (28.24%) subjects had cholelithiasis, 23(27.06%) subjects had cholecystitis, 4(4.71%) had cirrhosis of liver, 2(2.35%) had hepatic sequestration and 1(1.17) had acute hepatic crisis.

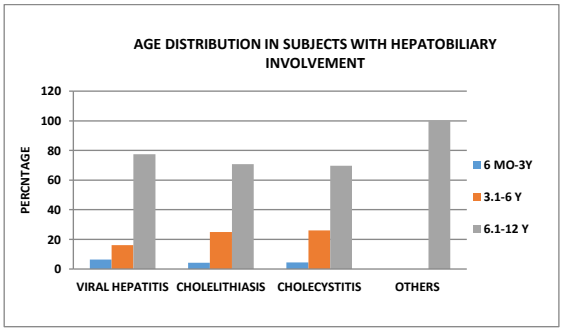

Figure 3: Age distribution in subjects with hepatobiliary involvement

Figure 3 shows age wise distribution of subjects with hepatobiliary involvement. In our study, out of 31 subjects having acute viral hepatitis maximum number of subjects i.e. 24 (77.42%) belonged to age group of 6.1-12 year followed by 5 (16.13%) subjects belonged to 3.1-6 years, 2 (6.45%) subjects belonged to 6 months -3 years age group. Out of 24 subjects having cholelithiasis maximum number of subjects i.e. 17 (70.83%) belonged to age group of 6.1-12 year followed by 6 (25%) subjects belonged to 3.1-6 years, 1 (4.17%) subject belonged to 6 months -3 years age group. Out of 23 subjects having cholecystitis maximum number of subjects i.e. 16 (69.57%) belonged to age group of 6.1-12 year followed by 6(26.08%) subjects belonged to 3.1-6 years, 1 (4.35%) subject belonged to 6 months -3 years age group. All subjects in others group belonged to 6.1-12 years age group. Overall it can be depicted that hepatobiliary involvement is seen more as the age increases.

Table 3: Clinical profile of subjects with hepatobiliary involvement.

Clinical profile	Distribution n=85							
	Viral hepatitis (n=31)		Cholelithiasis (n=24)		Cholecystitis (n=23)		Others (n=7)	
	No.	%	No.	%	No.	%	No.	%
Fever	28	90.3	1	4.1	23	100	1	14.28
Pallor	27	87	24	100	23	100	7	100
Icterus	31	100	24	100	23	100	7	100
Hepatomegaly	27	87	19	79.16	19	82.6	7	100
Spleenomegaly	18	58	13	54.16	13	56.52	4	57.1
Oedema	3	9.7	-	-	-	-	4	57.1
Bleeding manifestation	3	9.7	-	-	-	-	4	57.1
Hepatic failure	3	9.7	-	-	-	-	4	57.1
Ruq abdomen pain	31	100	15	62.5	23	100	3	42.8

Table 3 shows clinical profile of subjects with hepatobiliary involvement. In our study, out of 31 subjects having viral hepatitis all subjects i.e. 31 (100%) had icterus and right upper quadrant abdominal pain followed by 28 (90.3%)subjects had fever, 27 (87%) had pallor and hepatomegaly, 18 (58%) subjects had splenomegaly, hepatic failure in 3 (9.7%)subjects. Out of 24 subjects having cholelithiasis all subject's i.e. 24 (100%) had icterus and pallor followed by 19 (79.16%) subjects had hepatomegaly, 15 (62.5%) had right upper quadrant abdominal pain. Out of 23 subjects having cholecystitis all subjects i.e. 23 (100%) had icterus, pallor, fever and right upper quadrant abdominal pain and 19 (82.6%) subjects had hepatomegaly. Out of 7 subjects having cirrhosis of liver, hepatic sequestration and acute hepatic crisis all had pallor, icterus, hepatomegaly and only 4 had hepatic failure.

Table 4: Laboratory Profile in Study Subjects with Hepatobiliary Involvement.

Laboratory profile		Distribution n=85				
		Viral hepatitis n=31	Cholelithiasis N=24	Cholecystitis N=23	Others N=7	Total N=85
Elevated	Direct bilirubin	19 (61.29%)	24 (100%)	21 (91.3%)	7 (100%)	71 (83.52%)
	Indirect bilirubin	31 (100%)	21 (87.5%)	23 (100%)	7 (100%)	82 (96.47%)
Elevated AST		29 (93.54%)	22 (91.66%)	19 (82.60%)	7 (100%)	77 (90.58%)
Elevated ALT		29 (93.54%)	13 (54.16%)	20 (86.95%)	7 (100%)	69 (81.17%)
Elevated ALP		31 (100%)	24 (100%)	23 (100%)	7 (100%)	85 (100%)
Low total proteins		6 (19.35%)	11 (45.83%)	-	5 (71.43%)	22 (25.88%)
Deranged PT/INR		3 (9.6%)	-	-	4 (57.14%)	7 (9.4%)
HBsAg positive		5 (16.12%)	-	-	-	5 (5.8%)
Increased TLC		11 (35.48%)	20 (83.33%)	23 (100%)	5 (71.43%)	59 (69.41%)

In our study, indirect bilirubin was raised in all subjects having viral hepatitis, cholecystitis and in other group. Direct bilirubin was elevated in all subjects with cholelithiasis and in 91.3 % of subjects with cholecystitis. ALT was elevated in 93.54% of subjects with viral hepatitis. Out of 85 subjects having hepatobiliary involvement all had elevated ALP, 82 (96.47%) subjects had elevated indirect bilirubin, 71 (83.52%) had elevated direct bilirubin, 77 subjects had elevated AST, 69 (81.17%) had elevated ALT, 59 (69.41%) subjects had increased total leucocyte count, 7 had deranged PT/INR and 5

(5.8%) subjects were found to be positive for HBsAg. Total leukocyte count was increased in all subjects with cholecystitis and 20 (83.33%) subjects with cholelithiasis.

Table 5: Radiological Finding in Subjects with Hepatobiliary Involvement.

Radiological findings		Distribution (n=85)	
		Number	Percentage
Hepatomegaly		65	76.47
Liver parenchymal disease		31	36.47
Cholecystitis		23	27.05
Cholelithiasis		25	29.41
Others	Hepatic infarct	1	1.1
	Cirrhosis	4	4.7

This table shows distribution of radiological findings among subjects with hepatobiliary involvement. In our study, out of 85 subjects having hepatobiliary involvement maximum subjects i.e. 65 (76.47%)subjects had hepatomegaly followed by 31 (36.47%) subjects had liver parenchymal disease,25 (29.41%) subjects had cholelithiasis,23 (27.05%)subjects had cholecystitis,4 (4.7%) subjects had early cirrhotic changes and 1 (1.1%) had hepatic infarct.

Correlation of hepatobiliary involvement with severe crisis rate in last 1 year, blood transfusions in past and hospitalisations in last 1 year

Out of 85 subjects with hepatobiliary involvement 18 subjects had <3 crisis rate in last 1 year and 67 subjects had more than or equal to 3 crises in last 1 year. Out of 110 subjects without hepatobiliary involvement 104 subjects had <3 crises in last 1 year and 6 subjects had more than or equal to 3 crises in last 1 year. P value was calculated and found to be statistically highly significant ($p<0.0001$).

Correlation of hepatobiliary involvement with blood transfusions showed that out of 85 subjects with hepatobiliary involvement 12 subjects had < 3 blood transfusions in last 1 year and 73 subjects had more than or equal to 3 blood transfusions in last 1 year. Out of 110 subjects without hepatobiliary involvement 106 subjects had < 3 blood transfusions in last 1 year and 4 subjects had more than or equal to 3 blood transfusions in last 1 year. P value was calculated and found to be statistically highly significant ($p<0.0001$). In this study, out of 85 subjects with hepatobiliary involvement 20 subjects had ≤ 5 hospitalisations in last 1 year and 65 subjects had more than 5 hospitalisations in last 1 year. Out of 110 subjects without hepatobiliary involvement 97 subjects had ≤ 5 hospitalisations in last 1 year and 13 subjects had more than 5 hospitalisations in last 1 year. P value was calculated and found to be statistically highly significant ($p<0.0001$).

Correlation of hepatobiliary involvement with mean haemoglobin (Hb) and Serum ferritin level

Mean haemoglobin in study subjects with hepatobiliary involvement was 6.31±0.83 gm % and 7.89±0.87 in subjects without hepatobiliary involvement. P value was calculated and found to be statistically highly significant ($p<0.0001$).

Correlation of hepatobiliary involvement with serum ferritin showed that out of 46 subjects with normal ferritin level 12 had hepatobiliary involvement. Out of 35 subjects with increased ferritin level 34 had hepatobiliary involvement in our study. P value was calculated and found to be statistically highly significant ($p<0.0001$).

DISCUSSION

SCA can affect any part of the body but the hepatobiliary system is one of the most common organs involved principally in homozygotic patients and it occurs as a result of sickling and haemolysis, indirectly as a result of chronic haemolysis and multiple blood transfusions, iron overload, the superimposition of hepatitis by hepatotropic or non-hepatotropic viruses and by other infections.

Hepatobiliary complication of sickle cell disease can be viewed as follows.[4]

A) Clinical syndromes

a) Acute sickle hepatic crisis
b) Hepatic /reverse sequestration
c) Sickle cell intrahepatic cholestasis
   Acute sickle cell intrahepatic cholestasis
   Chronic intrahepatic cholestasis
   Benign hyperbilirubinemia
d) Miscellaneous
   Budd –chiari syndrome
   Hepatic infarction
   Hepatic abscess
   Hepatic biloma
   Zinc deficiency with hyperammonemia

B) Complications of chronic haemolysis and multiple transfusions

a) Cholelithiasis
b) Choledocholithiasis
c) Hepatic iron overload
d) Viral hepatitis, hepatitis B and C

It is unclear whether hepatic pathology specific to SS disease exists. There are several possible mechanisms of hepatic involvement which are as follows.

a) Sickled cells in sinusoids -phagocytosis by Kupffer cells-sinusoidal obstruction-anoxic necrosis of hepatic cells.[3]
b) Sickle cell in hepatic artery –hepatic infarcts and focal necrosis.[3]
c) Chronic haemolysis with accelerated bilirubin turnover-cholelithiasis or cholestasis.[3]
d) Factors associated with primary disease but related with transfusion therapy, hemosiderosis and viral hepatitis.[1,3,4]

Hepatomegaly
The incidence of hepatomegaly is more common in SS disease in comparison with trait. Hepatomegaly occurs in 40-80% of sickle cell patients. Usually liver is enlarged and smooth, firm, nontender. During painful crisis of the disease, further enlargement of liver occur.[4] Elevated serum level of GGT in SCA during steady state is suggestive of increased disease severity.[5] Alanine aminotransferase, alkaline phosphatase and bilirubin levels are significantly higher during crisis than at recovery, especially in young patient.[6]

Viral hepatitis:
A patient with SS disease more prone to viral hepatitis but it is unclear whether this is due to risk factors such as blood transfusion or due to an increased susceptibility. Acute viral hepatitis has the same clinical course in the sickling disorders as in the general population, other than a higher peak bilirubin level reflecting baseline haemolysis.[2,3]

Intrahepatic cholestasis
Acute sickle cell intrahepatic cholestasis is a rare but a serious and sometimes fatal complication of SCA. It results from severe obstruction of the liver sinusoids leading to stasis, hypoxia and intracanalicular cholestasis secondary to ballooning of the hepatocytes. Clinically, it resembles acute hepatic crisis but the main differentiating points is the associated extreme hyperbilirubinemia, coagulopathy and acute hepatic failure and renal impairment.[2,4] Plasma ALT, AST and alkaline phosphatase levels are very high. Prothrombin time and partial thromboplastin time are prolonged; blood urea, creatinine, and ammonia are elevated. Hypofibrinogenemia, thrombocytopenia, and lactic acidosis may accompany the liver failure. The characteristic finding is that of strikingly very high plasma bilirubin concentrations.[4] Early diagnosis, intensive supportive care including exchange blood transfusion, fresh frozen plasma, platelet transfusion and plasmapheresis may reverse the process of intrahepatic sickling and cholestasis resulting in a favourable outcome.[2] Chronic intrahepatic cholestasis is a mild benign condition characterised by prolonged hyperbilirubinemia in the absence of right upper guardant abdominal pain and evidence of haemolysis. It can be successfully treated with a regular exchange blood transfusion program with or without hydroxyurea.[2]

Acute sickle cell hepatic crisis
It occurs in approximately 10% of patients with sickle cell anaemia. Patients present with acute right upper quadrant pain, nausea, low grade fever, tender hepatomegaly, and jaundice. Plasma AST and ALT levels are raised because of severe hypoxic injury. The syndrome is self-limited and resolves within 3-14 days with intravenous hydration and analgesia.[2]

Hepatic sequestration crisis-
It is rare complication of SCD and it is caused by obstruction of the blood flow from the liver sinusoids by the sickled red blood cells leading to compression of the bile ducts. This leads to pooling of blood within the liver leading to acute hepatic enlargement. It is presents with right upper quadrant pain, increasing hepatomegaly, with a rapid drop in haemoglobin and haematocrit levels and an increase in the reticulocyte count and bilirubin level. This differentiates it from acute hepatic crisis. When treated with hydration and blood transfusion, it behaves like splenic sequestration with regression of the hepatic size and increase in haemoglobin level. Recurrence is common and it can also cause chronic hepatic sequestration. [2,4]

Cirrhosis
Cirrhosis of sickle cell disease is usually secondary to chronic hepatitis infection or to iron over load. Ferritin levels significantly correlate with number of transfusions.[7] The degree of liver iron overload is clearly associated with the number of previous blood transfusions. This will lead to liver fibrosis and, eventually, liver cirrhosis. It is unclear whether chronic hepatic ischemia or indeed that disease itself contributes to fibrogenesis.[2]

Hemochromatosis
Increases in serum ferritin occur during painful vaso-occlusive sickle crises and hence steady-state ferritin levels provide a better estimate of the degree of iron overload. In multi transfused patients, increased deposition of iron occurs within reticuloendothelial cells, including Kupffer cells. Mechanism of end organ damage in iron overload.[8]

Cholelithiasis
Cholelithiasis is one of the common complications of SCA. These are usually pigment stones that result from chronic haemolysis leading to increased bilirubin production.[2] Onset of cholelithiasis is as early as 2 to 4 years of age. Prevalence increases progressively with age reaching a frequency of nearly 30% by 18 years of age.[3]
Laparoscopic cholecystectomy is the treatment of choice in children with clinically symptomatic disease, but the best option for asymptomatic ones is still a source of debate. Elective LC should be the gold standard in children with SCD and asymptomatic cholelithiasis to prevent the potential complications of cholecystitis and choledocholithiasis which lead to major risks, discomfort, and a longer hospital stay.[9]

Choledocholithiasis
It is usually secondary to cholelithiasis but there is also primary choledocholithiasis. In the general population with cholelithiasis, the incidence of

common bile duct stones is reported as 10%-15%. In SCA the frequency of common bile duct stones is 18%-30%. It has been found that ERCP is valuable both as a diagnostic and therapeutic procedure for SCA patients with choledocholithiasis both pre and post laparoscopic cholecystectomy. This sequential approach of endoscopic sphincterotomy and stone extraction followed by laparoscopic cholecystectomy is safe and effective approach for the management of SCA patients with cholelithiasis and choledocholithiasis.[2]

Biliary sludge

This is one of the common complications of SCA, a sequel of chronic haemolysis, is a mixture of calcium bilirubinate and cholesterol crystals within viscous bile that contains a high concentration of mucus and proteins. It can be seen in the gallbladder or bile ducts. On ultrasound, it characteristically produces a low-amplitude echo pattern, intraluminal layers in the dependent part of the gallbladder. Patients with biliary sludge should be followed-up and those who develop gallstones should undergo elective laparoscopic cholecystectomy. Some patients who are symptomatic because of biliary sludge should be offered laparoscopic cholecystectomy to relieve them of their symptoms.[2]

Cholestasis

Cholestasis can occur when the hepatic vein pressure abruptly increases, exceeding the maximal bile secretory pressure of 20-mm Hg, as seen in chronic passive congestion, Budd-Chiari syndrome or biliary obstruction. It also results from drugs that affect the Na^+K^+ ATPase activity, such as phenothiazine's, androgens, oestrogens, or indomethacin that affect the bile-acid binding cytosolic proteins. In sepsis, endotoxin decreases bile flow.[3]

Cholecystitis

Cholecystitis is considered one of the most common hepatobiliary complications in patients with SCD, often occurring due to a gallstone obstruction or infections. It is likely that cholecystitis develops in the affected patients due to an infectious process. However, it may alternatively be caused by an obstructive gallbladder stone, or as a hepatobiliary crisis due to the sickling process.[10] Fever, nausea, vomiting and right upper quadrant abdominal pain are clinical feature with a wide differential diagnosis. The diagnosis is aided by delayed visualization of gall bladder in biliary scintigraphy. Treatment of acute cholecystitis does not differ from that of the general population and consists of antibiotics and general supportive care with consideration for elective cholecystectomy weeks after the acute episode subsides.[3]

Sickle cell cholangiopathy

Cholangiopathy is a consequence of sickling in the end arteries of the biliary arterial tree leading to hypoxia and dilatation. SCD patients have bile ducts dilatation limited to the common bile duct but there are also those who have dilatation involving both extra and intrahepatic bile ducts. These patients need to be followed up regularly for the possibility of developing bile duct stones; considering the high frequency of biliary sludge and the possibility of bile duct stones formation in these patients, endoscopic sphincterotomy may be beneficial as this may obviate the future development of bile duct stones.[2]

Abdominal imaging in sickle cell patients.[4]

Given the significant overlap in the clinical presentation of the various hepatobiliary syndromes in sickle cell patients, imaging studies are commonly performed and may help elucidate the specific or dominant pathophysiologic process.

Abdominal ultrasound-

Abdominal ultrasound in patients with sickle cell anaemia may reveal gallstones and increased echogenicity of the liver and pancreas caused by iron deposition. Ultrasound examination is less useful for evaluating left upper quadrant pain due to the frequent presence of artefacts from splenic calcifications have computerized tomography (CT) is the preferred mode of imaging in these situation.[4]

CT of the abdomen

CT scanning in homozygous patients with sickle cell anaemia usually reveals diffuse hepatomegaly, possibly a reflection of expansion of the hepatic reticuloendothelial system. Hepatic infarction with wedge-shaped areas of low attenuation, hepatic abscess (irregular low attenuation area with peripheral enhancement and air/fluid levels), iron overload, and retained common bile duct stones after cholecystectomy are among the noted abnormalities.[4]

MRI

MRI provides a qualitative assessment of hepatic iron overload in transfusion-dependent patients, showing decreased signal intensity in the liver, pancreas, and spleen before atrophy, caused by iron deposition. MRI can also provide a limited quantitative assessment of hepatic iron overload, being able to effectively separate patients with hepatic iron levels greater than100 µg/mg from these with levels less than 100 µg/mg. However, it is unable to differentiate between iron levels in the 100-400µg/mg range.[4]

Liver biopsy

Pathologic changes caused by concurrent chronic hepatitis B or C including portal triaditis, chronic interface hepatitis, or cirrhosis, and changes caused by cholestasis from common bile duct stones may be

seen in sickle cell patients. Findings primarily caused by sickle cell anaemia, which have been reaffirmed in several studies, include intrasinusoidal sickling with Kupffer cell hyperplasia with erythrophagocytosis, proximal sinusoidal dilatation, and hemosiderosis. Mild centrilobular necrosis has also been described in patients with sickle hepatic crises and widespread anoxic necrosis has been noted in post-mortem biopsies in patients with sickle cell intrahepatic cholestasis.[4] In a cross-sectional study done by Qhalib HA et al to describe the pattern of hepatobiliary complications among patients with (SCD) and to assess their correlation with age, gender and other risk factors. They found that hepatobiliary complications increased significantly with age and were notably higher among those who were often admitted to hospital and/or underwent frequent blood transfusions. We obtained similar results in our study.[10]

BOND LR et al in their study on Gall stones in sickle cell disease in the United Kingdom studied the prevalence of gall stones prospectively by abdominal ultrasound examination in 131 patients. They suggested that all patients with SCD should be screened routinely for gall stones and that elective cholecystectomy should be performed in those with symptoms or complications.[11]

A prospective study was carried out by Mahera MM et al aimed at finding out clinical, biochemical, and hepatic histological findings in SCD patients. They found that clinical spectrum of sickle cell disease ranges from mild liver function test abnormalities to significant hepatic abnormalities with marked hyperbilirubinemia. Similar results were seen in the present study.[12]

Limitations

- Work up to r/o primary liver pathology such as liver biopsy or viral markers were not done.
- Sample size is small. It needs further similar study with large sample size for its implication
- Patients were not followed up and hence it cannot predict long term residual hepatobiliary involvement or complication.
- Further study is necessary to define the mechanism of liver involvement in sickle cell disease.
- Serum ferritin was done only in 81 subjects out of 195 because of limited resources.

CONCLUSION

Hepatobiliary involvement is common complication in children with SCD requiring frequent blood transfusions, hospitalizations and having increased number of crisis rate.[13,14] Prevention of infections, immunization, balanced nutrition, folic acid & zinc supplementation, hydroxyurea may reduce rate of infections and blood transfusion & hospitalization thereby prolonging the onset of Hepatobiliary complications.[15,16] Monitoring for organ involvement from early years and management of complications may reduce long term morbidity and mortality in patients with SCD.

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How to cite this article: Bokade CM, Chauhan U, Dhole C. Study of Hepatobiliary Involvement in Children with Sickle Cell Disease. Ann. Int. Med. Den. Res. 2017; 3(3):PE09-PE15.

Source of Support: Nil, **Conflict of Interest:** None declared