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A Study on Acute & Chronic Hepatobiliary Manifestations of Sickle Cell Syndromes - Clinical, Biochemical, and Ultrasonographic Abnormalities

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Abstract: ***Background: Sickle cell disease (SCD) encompasses a group of hemoglobinopathies characterized by a single amino acid substitution in the beta - 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. Our study aims to identify the pattern of hepatobiliary manifestations in terms of presentation, clinical features, routinely available laboratory indices and abdominal ultrasonography and to asses the extent of morbidity and mortality among patients of sickle cell syndrome due to hepatobiliary abnormalities. Methods: a cross sectional observational study was performed among 100 diagnosed cases of sickle cell syndrome, from January 2021 to october 2022. Subjects of both sexes above 18 years were enrolled. Thorough history taking, full clinical examination, hematological and biochemical parameters assessment, and abdominal ultrasonographic studies were performed in all patients. Results: Hepatobiliary involvement was found in 60% of patients. Abdominal pain was the most common symptom. Pallor was the most common sign, followed by icterus. Cholelithiasis was the most common (40%) complication followed by biliary sludge (14%). Tender hepatomegaly was found in almost all patients of acute hepatic crisis. Acute hepatic crisis & acute hepatic sequestration were the most common causes of mortality. Conclusions: Clinical spectrum of sickle cell syndrome ranges from mild liver function test abnormalities in asymptomatic patients to significant hepatobiliary abnormalities with marked hyperbilirubinemia. Acute hepatic crisis & acute hepatic sequestration were the most common acute hepatobiliary manifestations encountered during the study and they were the frequent causes of mortality, acute hepatic sequestration even though it is rare, it is life threatening & associated with high mortality. Acute hepatobiliary complications were not found in patients of sickle cell AS pattern.***

Keywords: sickle cell syndrome, hepatobiliary

1. Introduction

Hemoglobinopathies are disorders affecting structure, function or production of hemoglobin. These conditions are usually inherited and range in severity from asymptomatic laboratory abnormalities to death in utero. Solubility and reversible oxygen binding are the key properties deranged in hemoglobinopathies. Sickle cell syndromes, one among the common hemoglobinopathies around world, are inherited as an autosomal recessive disorder caused by a point mutation in the beta globin gene of hemoglobin that changes the sixth amino acid from glutamic acid to valine (HbS). If the mutation affects only one beta globin chain, and the other is normal, the patient is said to have the sickle cell trait, which is relatively benign carrier state and doesn't have classical phenotypic features of sickle cell disease. When both beta chain carries HbS mutation, the patient exhibit phenotypic features of SCD [1]

Globally SCD affects 300000 infants every year, most prevalent in malaria endemic areas such as Middle - East, Africa and South Asia. It is estimated that 1in 365 African American children have SCD while 1 in 13 are born with sickle cell trait. Given the high prevalence and chronic nature of the disease, SCD is a very resource intensive disease, resulting in significant health care expenditure for both the society and individual. [2]

The sickle gene is widespread among many tribal population groups in India with prevalence of heterozygotes varying from 1 - 40 percent. Madhya Pradesh has the highest load with an estimated number of 9, 61, 492 sickle heterozygotes and 67, 861 sickle homozygotes. In Maharashtra, the sickle gene is widespread in all the eastern districts, also known as the Vidarbha region, in the Satpura ranges in the north and in some parts of Marathawada. The prevalence of sickle cell carriers in different tribes varies from 0 to 35 percent. [3]
The point mutation in the beta chain of hemoglobin leads to polymerization of the hemoglobin when the oxygen saturation is lowered, resulting in deformity of the red blood cells and microvascular occlusion. This as well as its subsequent effects including cellular dehydration, inflammatory response and reperfusion injury which are important pathophysiological mechanisms leads to the different manifestations of SCD. This venoocclusive components usually dominates the clinical course. Prominent manifestations include episodes of ischemic pain, and ischemic malfunctions or frank infarction of spleen, central nervous system, bones, joints, liver, kidneys and lungs. [4]

The gastrointestinal manifestations are usually due to small vascular infarcts and microvascular occlusion and ischemia presenting as abdominal crisis with severe pain, acute pancreatitis, peptic ulcer disease and rarely ischemic bowel. [5] Within the digestive tract, the hepatobiliary system is one of the most common intra - abdominal organs involved in SCD and hepatic involvement is observed in 10 - 40% cases of sickle cell crisis. [2]

The manifestations range from benign hyperbilirubinemia to overt liver failure. Hepatobiliary involvement in SCD can be divided into Acute and Chronic manifestations. The acute manifestations, which occurs with the spectrum of acute clinical presentations are often referred to as "Sickle cell hepatopathy". This is an umbrella term referring to liver dysfunction and hyperbilirubinemia due to intrahepatic sticking process during SCD crisis leading to ischaemia, sequestration and cholestasis. The chronic manifestations

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include cholelithiasis, choledocholithiasis, iron overload, viral hepatitis, sickle cell cholangiopathy. [2]

Clinically the diagnosis and appropriate management of hepatobiliary manifestations of SCD is challenging as they may present in a myriad ways along a spectrum from relatively benign such as biliary sludge to as lethal as acute liver failure. [2]
Due to the existing diagnostic and therapeutic dilemmas to treating physicians and considering the high prevalence of sickle cell cases in Vidarbha region [6] our aim is to identify the pattern of hepatobiliary manifestations in terms of presentation, clinical features, routinely available laboratory indices and abdominal ultrasonography and to asses the extent of morbidity and mortality among patients of sickle cell syndrome due to hepatobiliary abnormalities.

2. Methods

A cross sectional observational study was conducted among 100 diagnosed cases of sickle cell syndrome of age more than 18 years admitted in the medicine ward of Indira Gandhi Govt. Medical College from January 2021 to October 2022 who fulfilled the inclusion & exclusion criteria. Institutional ethical committee clearance obtained before the commencement of study.

Inclusion criteria: Males and females of Age > 18 years, diagnosed cases of sickle cell syndrome &those who gave informed consent.

Exclusion criteria: Chronic alcoholics, Chronic hepatotoxic drugs intake (antiTB drugs, NSAIDs etc), Pregnant females, Congenital hyperbilirubinemia, Non - sickle related viral hepatitis, Sickle beta thalassemia**,** patients of cirrhosis liver were excluded from the study.

Methodology: Patients were evaluated based on symptoms at the time ofadmission and hospital stay, clinical findings, laboratoryinvestigations, CBC and peripheral smear, LFTs, S. ferritin, INR, USS of liver and biliary system, complications associated & outcome.

Statistical analysis: All the data were tabulated, and then analysed with appropriate statisticalSoftware "SPSS 27th version''. Data were presented as a mean with standard deviation or proportions and Appropriate Mean, standard deviation and variance was calculated andappropriate statistical test of significance were applied.

3. Results

Most common pattern requiring hospitalisation among sickle cell syndrome was SS pattern (70%), AS pattern constituted30%. Mean age of patients was 25.8 with a standard deviation of 6.07 and a range of 18 to 44, most patients belongs to the age group of 21 - 30 & none of them were older than 50 years. Majority of patients were males (57%) & females constitutes 43%.

Abdominal pain was the most common symptom among patients of both SS & AS pattern, followed by breathlessness in SS pattern & joint pain in AS pattern. Pallor was the most common clinical sign among SS (52.8%) & AS (80%) pattern, followed by icterus (20% in both AS & SS pattern).15.7% of patients of SS pattern had hepatomegaly, 7.1% had right hypochondrial pain & 4.2% had splenomegaly.

Mean Hb was 5.6 with a standard deviation of 2.1gm%.80% Patients had normal SGOT/SGPT at the time of admission, 16% had values upto three times higher, 4% had values more than three times higher but less than 1000 IU, and none of them had values more than 1000IU, among SS pattern 21.4% patients had values up to the range of three times normal and 5.7% had a values more than three times higher, but less than 1000 IU, rest had normal values of SGOT/PT & among AS pattern 3.4 % had a value upto three times normal, rest had normal values OF SGOT/PT.92% of patients had normal serum ALP levels at admission, 8% of patients had ALP levels between 300 - 650 and none of them had ALP levels >650, all patients of AS pattern had normal S. ALP levels.82% of patients had a total bilirubin <4mg% at admission, 22% had values between 4 - 15mg%, & 6% had a value between 15 - 30mg% at admission. Prothrombin time was normal in all patients & none of them were seropositive for HBsAg & HCV in my study.

Hepatobiliary involvement was found in 60% of patients. Cholelithiasis was the most common hepatobiliary complication found in 40% of patients, biliary sludge was found in 14% patients, acute hepatic crisis was found in 13% patients, 4% each had splenic abscess & cholecystitis, 2% each had portal hypertension & choledocholithiasis, 1% had acute hepatic sequestration. Total Mortality encountered during study was 6%, of which 5% was due to acute hepatic crisis, & 1% was due to acute hepatic sequestration. The association between SGPT, S. ALP & S. total bilirubin with the hepatobiliary complication encountered was statistically significant. The association between mortality & SGPT, S. ALP & S. total bilirubin was found to be statistically significant.

	USG Findings	SS Pattern	AS Pattern	Percentage
Liver	Normal	52 (74%)	28	80%
	Hepatomegaly	12 (17.1%)	0	12%
	Fatty Liver	8 (11.4%)	2	8%
Intrahepatic Biliary Radicles	Normal	70 (100%)	30	100%
	Dilated	0 (0%)	0	0%
Extrahepatic Biliary Radicles	Normal	68 (97.1%)	30	98%
	Dilated	2 (2.9%)	0	2%
Gall Bladder	Normal	23 (33%)	10	33%
	Distended	04 (6%)	0	4%

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	Gb Sludge	9 (13%)	5	14%
	Single Calculi	3 (4%)	0	3%
	Multiple Calculi	32 (46%)	14	46%
	Polyps	0 (0%)	0	0%
Portal Vein	Normal	68 (97.1%)	30	98%
	Dilated	2 (2.8%)	0	2%
Spleen	Normal	54 (77.1%)	27	81%
	Autosplenectomy	2 (2.9%)	0	2%
	Postsplenectomy	2 (2.9%)	0	2%
	Splenomegaly	9 (12.9%)	2	11%
	Splenic Abscess	3 (4.3%)	1	4%

Figure 1: Distribution according to USG Findings

Complications	SS Pattern	AS Pattern	Percentage	P value
Cholelithiasis	27 (38.5%)	13 (43.3%)	40 (40%)	**0.087**
Biliary Sludge	9 (12.8%)	5 (16.7%)	14 (14%)	
Acute Hepatic Crisis	13 (18.5%)	0 (0%)	13 (13%)	
Splenic Abscess	2 (2.8%)	2 (6.7%)	4 (4%)	
Cholecystitis	4 (5.7%)	0 (0%)	4 (4%)	
Choledocholithiasis	2 (2.8%)	0 (0%)	2 (2%)	
Portal Hypertension	2 (2.8%)	0 (0%)	2 (2%)	
Acute Hepatic Sequestration	1 (1.4%)	0 (0%)	1 (1%)	
Normal	10 (14.2%)	10 (33.3%)	20 (20%)	
Total	70	30	100 (100%)	

Figure 2: Distribution according to Hepatobiliary Complications

Distribution according to Outcome

Diagnosis	No. of Patients	No & Percentage Of Survivors	No& Percentage of Non - Survivors
Cholelithiasis	40	40 (100%)	0 (0%)
Vaso - Oclusive Crisis	34	34 (100%)	0 (0%)
Cholecystis	4	4 (100%)	0 (0%)
Choledocholithiasis	2	2 (100%)	0 (0%)
Acute Hepatic Crisis	13	8 (61.5%)	5 (38.5%)
Acute Hepatic Sequestration	1	0 (0%)	1 (100%)
Portal Hypertension	2	2 (100%)	0 (0%)
Splenic Abscess	4	4 (100%)	0 (0%)
Total	100	94%	6%

Correlation Between Outcome & Liver Function Tests

Complication	NON SURVIVORS (6%)										
	S. SGPT LEVELS				S. ALP LEVELS			S. TOTAL BILIRUBIN			
	Normal	<3times Normal	>3times Normal - 1000 IU	>1000IU	<300IU	>300 - <650 IU	>650IU	<4mg%	4 - 15mg%	15 - 30mg%	>30mg %
Acute hepatic crisis (5%)	0	4	1	0	0	4	1	0	2	3	0
Acute hepatic sequestration (1%)	0	0	1	0	1	0	0	0	0	1	0
P Value	0.000				0.000			0.00			

4. Discussion

In our study Abdominal pain was the most common symptom among patients of SS pattern (37.1%) & AS pattern (33.3%). In SS pattern, 18.5%patients had breathlessness, 17.1% patients had joint pain, 12.8% patients had jaundice, 5.7% had fever, 2.8% had altered sensorium, 1.4% patients had vomiting. Among AS pattern 23.3% each patients had joint pain & breathlessness, 10% of them had fever, 3% had jaundice. The study done by Bokade [7], fever was found in 28.71% of patients, yellowish discoloration of urine and eyes in 61%, and right abdominal pain in 37.4%. In Johnson et al study, bone pain was present in 72% of patients and fever in 34%. So, the most common presentation was joint pain, abdominal pain and breathlessness are frequent symptoms in patients of sickle cell syndrome. [8] [9]

In our study Pallor was the most common clinical sign among SS (52.8%) & AS (80%) pattern, followed by icterus (20% in both AS & SS pattern).15.7% of patients of SS pattern had hepatomegaly, 7.1% had right hypochondrial pain & 4.2% had splenomegaly. Dalia et al study pallor was found in 84 %, and in the Sarkar study [10], it was 70%. In the Bokade study, jaundice was found in 45%, and in the Johnson et al study, it was found in 62%. [8]

In the study 36% each of patients had mild&moderate anemia, 24% had severe anemia, 13% had very severe

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anemia. Mean Hb was 5.6 with a standard deviation of 2.1gm%. In Mahebba et al study, it was 9.3gm/dl.

In my study 80% Patients had normal SGOT/SGPT at the time of admission, 16% had values upto three times higher, 4% had values more than three times higher but less than 1000 IU, and none of them had values more than 1000IU. In study conducted by Mohanty AP et al, [11] 40% of our patients had a two to three - fold rise in ALT level, while 42% had three folds rise in serum AST levels. Thirty - one percent of the patients had normal enzymes while 21% had the three enzymes deranged, 15.9%, 43% and 61.2% had abnormal ALT, AST and ALP respectively was found in a study conducted by Maher et al [12]. In a study conducted by BERRY et al [13] stated a mild to moderate transaminitis (median, 144 U/L; range, 27–630 U/L) in patients as a chronic hepatobiliary manifestation.

92% of patients had normal serum ALP levels at admission, 8% of patients had ALP levels between 300 - 650 and none of them had ALP levels >650.

82% of patients had a total bilirubin <4mg% at admission, 22% had values between 4 - 15mg%, & 6% had a value between 15 - 30mg% at admission. In study conducted by Mohanty AP et al [11], total bilirubin levels were elevated in 60%, while direct bilirubin levels were above the normal range in 40% of the cases. In Dalia et al study, serum total bilirubin was elevated in 42% patients and direct bilirubin in 50 % of patients.

In our study Liver was normal in 80% of patients, 12% had hepatomegaly & 8% had fatty liver. Intrahepatic biliary radicles were normal in all patients, 98% had normal extrahepatic biliary radicles and 2% had dilated extrahepatic biliary radicles.32% had normal gall bladder, 46% had multiple calculi, 15% had GB sludge, 4% had distended gall bladder &3% had single calculi. Portal indices were normal in 98% of patients & portal vein was dilated in 2% patients. Spleen was normal in 81% of patients, 11% had splenomegaly, 4% had splenic abscess & 2% each had autosplenectomy & postsplenectomy status.

In a study conducted by Mohanty AP et al [11], only 21 of the 100 performed ultrasounds were normal, similar to study by Mohanty et al [14] ultrasound was normal in 20 % of patients. Hepatomegaly was found in 37% of patients. In study by Dalia and Almeida [15], who found hepatomegaly in 34.3% and 30.4% subjects respectively, but study by Oparinde et al [16] and Papadaki found hepatomegaly in 70% of patients. Splenomegaly was the common sonographic feature of Mohanty AP et al study [11]. In, Mohanty AP et al study gall stones were detected in (14%). In Mohanty et al study [14], there were 10 % of patients who had gall bladder sludge, which is similar to studies by Mahebba (12 %) and Dalia (14%).

In our study Cholelithiasis was the most common hepatobiliary complication found (40%), biliary sludge was found in 14% patients, acute hepatic crisis was found in 13% patients, 4% each had splenic abscess & cholecystitis, 2% each had portal hypertension & choledocholithiasis, 1% had acute hepatic sequestration.20% patients had no hepatobilary complications. In study by Mohanty AP et al [11] 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. In 9% of patients in Mohanty AP et al study, the acute hepatic crisis was diagnosed, which was similar to study done by Ebert et al (10%) and 9% by Sarkar [10], but on the contrary, it was found only in 2% by Dalia and 1% by Bokade [7].1% of patients had a hepatic sequestration crisis in their study similar to the studies of Bokade et al [7], 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.

5. Conclusions

Clinical spectrum of sickle cell syndrome ranges from mild liver function test abnormalities in asymptomatic patients to significant hepatobiliary abnormalities with marked hyperbilirubinemia. Abdominal pain was found to be the most common presenting symptom, followed by breathlessness & joint pain, Pallor was the most common clinical sign, followed by icterus & hepatomegaly was a consistent clinical finding in patients of acute hepatic crisis. Acute hepatobiliary complications were not found in patients of sickle cell AS pattern. Cholelithiasis was the most common hepatobiliary complication encountered followed by biliary sludge & acute hepatic crisis. Acute hepatic crisis & acute hepatic sequestration were the most common acute hepatobiliary manifestations encountered during the study and they were the frequent causes of mortality, acute hepatic sequestration even though it is rare, it is life threatening & associated with high mortality. No mortalities were found from chronic hepatobiliary complications. Clarifying the dominant etiologic consideration during a crisis requires a thorough understanding of the various syndromes unique to this disorder and a comprehensive workup, including serologic testing and abdominal imaging. Continuous hepatic evaluation including periodical liver function tests, serological tests, ferritin levels and abdominal ultrasound should be performed & initiation of specific therapy, if indicated, for viral hepatitis or iron overload, and ‘anti - sickling’ treatments, may prevent chronic hepatopathy in this population.

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