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MINIREVIEWS

Acute and chronic hepatobiliary manifestations of sickle cell disease: A review

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Abstract

Sickle cell disease (SCD) is a common hemoglobinopathy which can affect multiple organ systems in the body. Within the digestive tract, the hepatobiliary system is most commonly affected in SCD. The manifestations range from benign hyperbilirubinemia to overt liver failure, with the spectrum of acute clinical presentations often referred to as "sickle cell hepatopathy". This is an umbrella term referring to liver dysfunction and hyperbilirubinemia due to intrahepatic sickling process during SCD crisis leading to ischemia, sequestration and cholestasis. In this review, we detail the pathophysiology, clinical presentation and biochemical features of various acute and chronic hepatobiliary manifestations of SCD and present and evaluate existing evidence with regards to management of this disease process. We also discuss recent advances and controversies such as the role of liver transplantation in sickle cell hepatopathy and highlight important questions in this field which would require further research. Our aim with this review is to help increase the understanding, aid in early diagnosis and improve management of this important disease process.

Key words: Sickle cell disease; Hepatopathy; Hepatobiliary; Intrahepatic cholestasis; Hepatic sequestration; Sickle cell hepatic crisis; Sickle cell cholangiopathy; Liver transplant; Iron overload

Core tip: This review: (1) identifies the pathophysiology, common clinical and biochemical features of a spectrum of hepatobiliary manifestations in sickle cell disease; (2) presents the current evidence of role of liver transplant in

end stage liver disease due to sickle cell hepatopathy; and (3) identifies important areas of future research to explore unanswered questions regarding sickle cell hepatopathy.

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INTRODUCTION

Sickle cell disorder is an umbrella term involving all pathologies where hemoglobin S mutation is present on at least one beta chain. Hemoglobin A, also known as normal adult hemoglobin, comprises two alpha and two beta chains ($\alpha 2\beta 2$), with small amount of HbA2 ($\alpha 2\delta 2$) and HbF ($\alpha 2\gamma 2$). When there is a point mutation on beta chain with a substitution of valine for glutamic acid at the 6th position, it leads to formation of Hemoglobin S ($\alpha 2/\beta S2$). HbS has a sticky patch at the site of valine substitution which allows it to bind to other HbS molecules particularly in the deoxygenated state forming long chain polymers, resulting in distortion of erythrocytes causing sickling and increased hemolysis[1]. In the oxygenated state, although the sticky patch persists, the complementary receptor site is masked and cannot attach to deoxygenated HbS and polymerize. Hence if kept oxygenated, sickling can be prevented despite high concentration of HbS. Following recurrent sickling, subsequent pleiotropic effects include changes in red cell membrane structure and function, disordered red blood cell (RBC) volume control, increased RBC adherence to vascular endothelium misregulation of vasoactivity, and inflammation finally leading to vaso-occlusion and hemolysis.

If the mutation affects only one β globin chain and the other is normal, the patient is said to have the sickle cell trait, which is a relatively benign carrier state and does not have the classic phenotypic features of sickle cell disease (SCD). When both β chains carry HbS mutation, the patient exhibits phenotypic features of SCD which may include recurrent painful crisis, anemia, infections, stroke, organ failure and premature death due to various complications and end organ damage.

Sickle cell disease (SCD) is widely prevalent in the United States affecting about 100000 Americans[2]. Among different races, it is most common in African Americans. It is estimated that 1 in 365 African American infants have SCD while 1 in 13 has are born with the Sickle cell trait. The 2010 nationwide Center for Disease Control (CDC) survey of state newborn screening programs which screen for sickle cell trait (SCT) reported that incidence of SCT was 73.1 cases per 1000 black infants screened, 3.0 cases per 1000 white infants screened and 2.2 cases per 1000 Asian, Native Hawaiian or other Pacific Islander infants screened[3].

Given the high prevalence and the chronic nature of the disease, SCD is a very resource intensive disease, resulting in significant healthcare expenditure for both the society and the individual. A recent study done on Medicaid patients suggested an average cost of approximately $2500 per patient per month in total SCD direct and indirect care[4]. Globally SCD affects 300000 infants every year, most prevalent in areas which are endemic for malaria such as Middle-East, Africa and south Asia. It is also estimated that in many African countries, 10%-40% population carries sickle cell trait resulting in about a 2% prevalence of SCD in these countries[5].

HEPATOBILIARY MANIFESTATIONS OF SCD

SCD can involve multiple organ systems including the gastrointestinal tract. These gastrointestinal manifestations usually occur 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[6,7]. 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[8-10].

Clinically, the diagnosis and appropriate management of hepatobiliary manifestations of SCD is challenging as they may present in myriad ways along a spectrum from relatively benign such as gallbladder sludge to as lethal as acute liver failure. The objective of this review is to describe the hepatobiliary manifestations of sickle cell disease with emphasis on their pathophysiology and clinical manifestations. We also organize and discuss existing clinical terminologies used to describe these hepatobiliary manifestations.

CLASSIFICATION

Hepatobiliary involvement in SCD can be divided into acute manifestations (Table 1) occurring during vaso-occlusive crisis and chronic manifestations (Table 2) which persist and may progress outside of the crisis state. It is important to understand that a spectrum of clinical manifestations may be observed for the same underlying pathophysiology depending on severity of vaso-occlusive crisis and the residual physiologic hepatic reserve. Sickle cell hepatopathy is an umbrella term defined as liver dysfunction and hyperbilirubinemia due to intrahepatic sickling process during SCD crisis leading to ischemia, sequestration and cholestasis[11]. While recurrent acute damage can eventually turn to more chronic liver disease in SCD, slow progressive liver damage can also independently lead to chronic liver disease (CLD) in absence of recurrent acute

Table 1 Acute hepatobiliary manifestations of sickle cell disease

Acute manifestations of SCD	Clinical presentation	Biochemical changes			Management
		Transaminase (AST, ALT) levels	Bilirubin	Alkaline phosphatase	
Acute sickle cell hepatic crisis	Fever, acute onset RUQ pain, jaundice and tender hepatomegaly	Normal to 3 × upper normal	Upto 15 mg/dL, mainly conjugated	Normal to slight elevation	Supportive with treatment of SCD crisis
Acute Hepatic sequestration	Acute onset RUQ pain, hepatomegaly and anemia	Normal	Upto 24 mg/dL, mainly conjugated	Can go upto 650 IU/L	Supportive with blood or exchange transfusion
Acute intrahepatic cholestasis	Fever, RUQ pain rapidly progressing to acute liver failure	Elevated usually > 1000	Elevated in 100 s, mostly conjugated	Normal or elevated > 1000 IU/L	Supportive, exchange transfusion, correction of coagulopathy? Liver transplant

SCD: Sickle cell disease; AST: Aspartate transaminase; ALT: Alanine transaminase; RUQ: Right upper quadrant.

Table 2 Chronic hepatobiliary manifestations of sickle cell disease

Chronic hepatobiliary manifestations of SCD	Clinical presentation	Biochemical changes			Management
		Transaminase (AST, ALT) levels	Bilirubin	Alkaline phosphatase	
Cholelithiasis	RUQ pain, fever, jaundice	Normal or elevated	Normal or elevated	Normal	Cholecystectomy
Choledocholithiasis	RUQ pain, fever, jaundice, cholangitis	Normal or elevated	Elevated	Elevated	ERCP
Iron overload	Asymptomatic elevated LFTs to frank cirrhosis	Normal or elevated	Normal to mild elevation	Normal	Iron chelation
Viral hepatitis	Viral prodrome, fever, hepatomegaly, jaundice	Acute-elevated Chronic-normal or elevated	Acute-elevated Chronic-normal or elevated	Acute - normal to slightly elevated; Chronic - mostly normal	Based on AASLD guidelines
Sickle cell cholangiopathy	Obstructive jaundice, itching, cholestatic LFTs	Normal or elevated	Elevated	Elevated	ERCP liver transplant

SCD: Sickle cell disease; AST: Aspartate transaminase; ALT: Alanine transaminase; RUQ: Right upper quadrant; ERCP: Endoscopic retrograde cholangiopancreatography; LFTs: Liver function tests; AASLD: American Association for the Study of Liver Diseases.

manifestation.

ACUTE LIVER INVOLVEMENT IN SICKLE CELL VASO-OCCLUSIVE CRISIS (SICKLE CELL HEPATOPATHY)

The underlying pathophysiology for this disorder is wide spread sickling of erythrocytes during crisis. Intrahepatic sickling of erythrocytes leads to sinusoidal obstruction. Depending upon the degree of sickling and severity of sinusoidal obstruction, sickle cell hepatopathy can manifest in the following forms.

Acute sickle cell hepatic crisis

Acute sickle cell hepatic crisis has been reported in about 10% of patients presenting with vaso-occlusive crisis[12]. Clinically, this may present similar to acute cholecystitis with acute onset of fever, right upper quadrant abdominal pain and jaundice. Tender hepatomegaly which is commonly observed differentiates this from acute cholecystitis.

Pathophysiology: The underlying mechanism for this entity is believed to be due to sickled erythrocytes causing sinusoidal obstruction. This obstruction can cause transient liver ischemia and in severe cases can lead to infarction. On histology, sickle cell aggregates are observed in sinusoidal spaces. Depending on severity of the vaso-occlusive crisis, kupffer cell hypertrophy and in most severe cases, severe centrilobular necrosis can also be observed[13].

Biochemical abnormalities: The biochemical abnormalities observed vary and in most cases do not correlate with the severity of insult or even histological findings[14]. Serum transaminases - alanine transaminase (ALT), aspartate transaminase (AST) are usually 1-3 times elevated from the normal although levels in the thousands have been reported. The transaminase levels also fall rapidly followed by resolution of crisis unlike viral hepatitis where transaminases are elevated for a prolonged time. Serum bilirubin is elevated with a predominantly conjugated fraction but usually stays < 15 mg/dL[13]. Biochemical abnormalities resolve within 3-14 d.

Treatment: Treatment is usually supportive with rehydration and oxygenation similar to acute vaso-

occlusive crisis.

Acute hepatic sequestration

This entity is less commonly observed in SCD crisis[14]. The underlying mechanism is sequestration of large amount of erythrocytes in the spleen, pulmonary vasculature and rarely in the liver. Patients usually present with abrupt onset of severe right upper quadrant (RUQ) pain, rapidly evolving hepatomegaly and acute rapidly worsening anemia. Depending on amount of erythrocyte consumed in reticuloendothelial system, patients can also present with acute symptomatic anemia, shock rapidly progressive towards mortality. There is usually an acute fall in hematocrit and this fall coincides with acute hepatomegaly[15]. Falling hematocrit is also associated with appropriate rise in reticulocyte count. Smooth but remarkable hepatomegaly is often observed.

Pathophysiology: There is sequestration of large amount of erythrocytes in the spleen, pulmonary vasculature and to a small extent in the liver. The trapped sickled erythrocytes due to Kupffer cell erythrophagocytosis cause massive dilation of sinusoids which exert mass effect and causes compression of biliary tree[14]. Biopsy shows dilated sinusoids and trapped erythrocytes. Intrahepatic cholestasis and bile plugs are also commonly observed but necrosis is uncommon.

Biochemical abnormalities: Biochemical abnormalities usually include significant hyperbilirubinemia which can go as high as 24 mg/dL. The elevated bilirubin is mainly in conjugated form abiding to obstructive pathophysiology of the disease. Alkaline phosphatase can also be elevated and can rise as high as 650 IU/L. Transaminases are usually within normal limits.

Treatment: Treatment is usually supportive. Simple blood transfusion or exchange transfusion to support tissue oxygenation usually suffices. A consideration in treatment of acute sequestration crisis is that resolution of this condition usually happens in 3-4 d and acute rise in hematocrit can be observed indicating not all the trapped erythrocytes are hemolyzed. Close monitoring of patient's hematocrit is required as rapid rise in resolution phase can increase the hyperviscosity of blood[16]. An increase in mortality due to heart failure, cerebrovascular accident (CVA) and even acute coronary syndrome (ACS) has been reported due to hyperviscosity[16]. If rapid rise in hematocrit is observed in the resolution phase, phlebotomy should be considered.

Acute intrahepatic cholestasis

Acute intrahepatic cholestasis is the most severe acute hepatic manifestation of SCD and can be fatal. Fortunately, it is very rare with total of only 17 reported cases so far[17]. It presents initially as severe acute hepatic crisis with fever, leukocytosis, RUQ abdominal pain, jaundice but can progress rapidly to multi-organ failure including renal failure and acute liver failure manifesting as encephalopathy (confusion) and bleeding diathesis (coagulopathy).

Pathophysiology: The pathophysiology of this fatal entity is diffuse sickling in the sinusoids leading widespread ischemia. Hypoxia leads to ballooning of hepatocytes and intracanalicular cholestasis. Widespread dilated sinusoids with intrahepatic cholestasis are seen on histology. In more severe cases, widespread anoxic necrosis with areas of acute and chronic inflammation are also seen[18].

Biochemical abnormalities: Biochemical evidence shows significantly elevated bilirubin levels which are mainly due to rise in conjugated component. Levels as high as 273 mg/dL have been reported[19]. This extreme hyperbilirubinemia is due to combination of hemolysis causing unconjugated hyperbilirubinemia, and intrahepatic cholestasis and renal impairment contributing to the conjugated component. Transaminase levels above 1000 mg/dL are commonly seen. Alkaline phosphatase can be normal or elevated but levels greater than 1000 IU/mL are rarely observed[19]. Hepatic dysfunction with derangement of coagulation profile in form of elevated prothrombin time (PT), partial thromboplastin time (PTT), International normalized ratio (INR) as well as hypofibrinogenemia are also observed.

Treatment: Rigorous supportive measures, exchange transfusion and correction of coagulopathy with fresh frozen plasma (FFPs) are proposed treatment measures[17,19]. This entity carries extremely high mortality. Renal impairment is thought to be due to primary hepatic impairment and few cases might require temporary dialysis. With correction of hepatic abnormality, renal function usually improves.

Overt liver failure without histologic changes

Although exceedingly rare, this entity is fatal and in absence of option for transplant carries extremely high mortality. There are isolated case reports to small case series reported describing acute liver failure in SCD[20,21]. While clinical presentation of acute liver failure (ALF) is similar to non SCD patients - acute onset liver dysfunction along with encephalopathy and coagulopathy, abdominal pain, tender hepatomegaly, ALF in SCD presents with extremely high Serum Bilirubin and PT[22], with relatively mild elevation in transaminases. Few cases where liver biopsy was performed showed centrilobular necrosis and very infrequently showed cholestasis.

Role of zinc deficiency

Zinc is a cofactor for ornithine transcarbamylase, an enzyme required in urea cycle[23]. Zinc deficiency has been suggested as a strong factor when hepatic failure is observed in SCD patients without significant histologic findings on biopsy. In ambulatory setting SCD patients who tend to have high ammonia levels have shown

reduction in Ammonia level on zinc supplementation. It is hypothesized that zinc deficiency predisposes these patients to higher risk of hepatic encephalopathy. Measurement and supplementation of zinc if low is recommended to prevent hepatic encephalopathy (HE)[24].

CHRONIC HEPATOBILIARY MANIFESTATIONS OF SICKLE CELL DISEASE

Viral hepatitis

Patients with SCD can present with acute or chronic viral hepatitis. Patients with SCD have a higher prevalence of both acute and chronic viral hepatitis due to exposure to risk factors like multiple transfusions *etc*. Prevalence of viral hepatitis in these patients also depends upon factors such as local prevalence of chronic viral hepatitis, transfusion protocols as well as vaccination practices. Some studies have shown that asymptomatic persistent elevation of ALT/AST in the absence of sickle cell crisis, is commonly associated with chronic hepatitis on liver biopsy[25].

Clinical presentation: Patients with acute viral hepatitis present similar to general population with malaise, jaundice and abdominal pain with tender hepatomegaly. Patients with chronic viral hepatitis are usually asymptomatic with incidentally discovered persistently elevated transaminases or may present with new diagnosis of cirrhosis and are found to have chronic viral hepatitis.

Biochemical abnormalities: Similar to non-sickle cell disease patients, acute viral hepatitis in SCD patients is associated with very elevated transaminase levels (usually 500-1000 IU/mL). In SCD patients however, the total serum bilirubin has been observed to be much higher than non SCD patients and ranges from 8-64 mg/dL with an average of 45 mg/dL[9].

Chronic Hepatitis can present with variable degree of transaminase elevation based on disease activity. As mentioned previously, most patients are asymptomatic and are diagnosed on workup of persistently elevated transaminases[25].

Liver biopsy if performed, in these cases reveals balloon cells with cellular derangement and leucocyte infiltration suggestive of viral hepatitis.

Treatment recommendations for viral hepatitis remain similar to AASLD guidelines in general population.

Transfusion iron overload

Hemosiderosis resulting from iron overload from recurrent blood transfusion is not uncommon in SCD and can lead to cirrhosis. It is as a consequence of accumulation of transfused iron, increased gastrointestinal absorption of iron due to intensive erythropoiesis and iron deposition as a result of continuous hemolysis[12]. Saturation of transferrin by excess circulating iron results in formation of reactive oxygen species (ROS) such as hydroxyl radicals. Excess iron tends to deposit in the hepatic parenchyma, endocrine organs, and in cardiac myocytes causing end organ damage by ROS-medicated lipid peroxidation[26].

Clinical presentation: Initially patients with moderate iron overload may present with abnormal liver biochemical tests (mostly hepatocellular) without any other clinical symptoms suggestive of liver disease. However, as the disease advances to cirrhosis, patients present with stigmata of chronic liver disease such as ascites, gastrointestinal bleeding, hepatosplenomegaly and thrombocytopenia. Encephalopathy and coagulopathy signify advanced liver disease. These features along with cardiac and endocrine involvement suggest iron overload as an etiology of liver disease. Physicians should be aware of cardiac and endocrine manifestations of iron overload such as symptoms of heart failure including orthopnea, paroxysmal nocturnal dyspnea or lower extremity swelling as well as endocrine abnormalities including decreased libido, diabetes mellitus, delayed puberty or delayed growth[26].

Pathophysiology: With multiple blood transfusions, increased deposition of iron occurs within the reticuloendothelial cells, including Kupffer cells. In a study by Brittenham *et al*[27], it was reported that patients diagnosed with either thalassemia major or SCD frequently had hepatic iron concentrations above 400 micromoles per gram which is the approximate "toxic threshold" that has been proposed for the development of hepatic fibrosis in patients with hereditary hemochromatosis[28]. In an autopsy study of 70 patients, Bauer *et al*[29] reported that micronodular cirrhosis with hemochromatosis, due to blood transfusion, was present in three patients and parenchymal iron accumulation not severe enough to cause fibrosis or inflammation was present in 30 others. Massive iron accumulation can lead to peri-cellular and portal fibrosis which can lead to diffuse fibrosis and ultimately cirrhosis.

Biochemical abnormalities: The gold standard for assessing liver iron stores in the absence of cirrhosis is Hepatic Iron Concentration (HIC), determined by liver biopsy and atomic absorption spectrophotometry[30]. Normal HIC is between 0.4 and 2.2 mg/g of liver dry weight. Based on data from hereditary hemochromatosis, less then 7 mg/g is not associated with obvious hepatic pathology while 15 mg/g is consistently associated with liver fibrosis[28].

Serum ferritin can be used as a surrogate marker in sickle cell anemia with repeated blood transfusions to provide an indirect estimate of body iron stores. During vaso-occlusive crises, serum ferritin increases and therefore steady-state levels obtained on multiple occasions outside SCD crisis gives a better estimate of the degree of iron overload[31]. Analysis of chronically

transfused SCD patients without viral hepatitis from STOP and STOP2 trials, showed that a ferritin level < 1500ng/mL was correlated with low transfusion burden and low measured Hepatic Iron Content (HIC), while a ferritin > 3000 ng/mL was consistently predictive of HIC > 10 mg/g. Thus, it can be inferred that serum ferritin may not be an accurate predictor of liver iron stores in the range of 1500-3000 ng/mL[32].

Magnetic resonance imaging (MRI) using Ferriscan (biomagnetic liver susceptometry) when available is preferred to estimate iron content of liver in patients receiving multiple blood transfusions. Liver biopsy is reserved for cases where MRI appearance is not consistent with transfusion history or suspicion for iron overload remains high in light of negative MRI study[33].

Treatment: Iron chelation with intravenous or subcutaneous deferoxamine is the first line therapy. This results in increased urinary and biliary excretion of iron and results in a meaningful decrease in serum ferritin and plasma ALT levels. Recommendation from American Academy of Pediatrics suggest to use chelation to maintain serum ferritin < 1500 ng/mL and HIC < 7 mg/g[34]. Some experts suggest performing annual liver MRI and initiate chelation when HIC > 3 mg/g or Serum Ferritin is > 1000 ng/mL on 2 or more occasions[33,35].

Gallstone disease

Cholelithiasis is fairly common in patients with homozygous SCD, with a an Incidence of 26%-58% in patients aged 10-65 compared to 17% in patients with SC-Hb C disease and SC-β thalassemia[36-38].

Pathophysiology: Gallstones are commonly made of the black rather than the brown pigment as a result of elevated bilirubin excretion[12]. Increased unconjugated bilirubin excretion resulting from catabolic breakdown of heme, bilirubin precipitation and the growth of bilirubinate crystals are determinant factors for the formation of gallstones. Up to 50% of gallstones in patients with SCD can be seen on plain films because calcium bilirubinate, which is the main component of these black stones, is radio-opaque[39].

Clinical presentation: Cholelithiasis: Like the general population, most patients with gallstones are asymptomatic. Intermittent abdominal pain related to fatty food can be elicited in history. Frequently, it goes unnoticed except when patient presents with acute cholecystitis or choledocholithiasis.

Acute cholecystitis: Presentation of acute cholecystitis is similar to the general population. Usual symptoms are abdominal pain, nausea, vomiting, fever and/or jaundice. Oftentimes it is challenging to differentiate from sickle cell hepatic crisis in patients with SCD. Imaging as well as recognition of pattern of acute hepatic crisis in such cases can help to differentiate these two entities.

Choledocholithiasis: Incidence of both asymptomatic and symptomatic choledocholithiasis (CDL) in SCD can range from 19%-26% which is comparable to the incidence found in patients with cholesterol gallstones[40]. However, bilirubin stones may frequently be asymptomatic as they only produce low grade obstruction because of their small size and friability. However, if significant obstruction persists they present with right upper quadrant or epigastric pain and jaundice. Presence of fever in this setting may suggest cholangitis and require emergent biliary decompression.

Biochemical abnormalities: Cholecystitis: Patients with acute cholecystitis may present with acute leukocytosis (with increased number of bands). Mild transaminitis can also be observed though serum bilirubin and alkaline phosphatase are usually normal.

Choledocholithiasis: Depending upon degree of obstruction, elevation of bilirubin, alkaline phosphatase with mild transaminitis are observed. These laboratory abnormalities are not very specific in patients with sickle cell disease. Even though serum bilirubin or transaminases are not associated with CDL in SCD, incremental hyperbilirubinemia (with levels higher than 5 mg/dL) is a better predictor of CDL than is bile duct dilation or elevation in either alkaline phosphatase or serum aminotransferase levels. This interestingly differs from cholesterol CDL in which increased levels of alkaline phosphatase and biliary duct dilation are good predictors[12].

Imaging: Ultrasound is less useful to appropriately make the diagnosis in patients with acute cholecystitis. Tc99m diisopropyl-iminodiacetic acid scan might show prolonged non-visualization of the gallbladder consistent with acute cholecystitis or more commonly, delayed visualization consistent with chronic cholecystitis. On the contrary, hepatobiliary radionuclide scans can safely rule out acute calculous cholecystitis when the gallbladder is visualized. Diagnosis of CLD can be established based on Ultrasound (US), but frequently cross-sectional images such as CT scan and/or MRI abdomen are required.

Treatment: Cholecystectomy is the most common surgical procedure in patients with SCD, comprising about 40% of the procedures on SC patients[41]. It should be pursued in patients with symptomatic gallstones and when there is difficulty distinguishing it from sickle cell hepatic crisis. However, in asymptomatic patients, it has become a controversial practice. Some authors advocate for early cholecystectomy taking into consideration complications of emergency surgeries, lack of clinical correlation of histologically chronic cholecystitis with clinical symptoms and finally, simplification of medical management by eliminating gallstones as a diagnostic possibility[12]. In contrast other authors believe that patients might not develop symptomatic biliary tract disease and therefore prophylactic cholecystectomy's risks might outweigh its benefits. The perioperative mortality rate of elective cholecystectomy has been reported to be 1% and the

Table 3 Current evidence of liver transplantation in sickle cell disease

Author	Number of patients	Outcomes
Hurtova *et al*[46]	6	1, 3, 5, and 10-yr survival rates were 83.3%, 66.7%, 44.4%, and 44.4%, respectively
Mekeel *et al*[48]	3	Patient and graft survival was 66%
Baichi *et al*[49]	2	100% mortality in post-transplant period due to multiorgan failure
Emre *et al*[50]	1	Failure of graft in 5 mo due to SCD crisis
Greenberg *et al*[51]	1	Successful but follow up only till day 28
Kindscher *et al*[52]	1	Successful with extrahepatic complications
Lang *et al*[53]	1	Successful at 6 mo
Ross *et al*[54]	1	Successful at 22 mo - death due to PE
van den Hazel *et al*[55]	1	Successful at 5.5 yr
Gilli *et al*[56]	1	Successful at 2 yr
Berry[57]	1	Death in post-op period

rate of postoperative complications to be more than 30%[41,42]. If choledocholithiasis is present, the common bile duct should be cleared of the gallstones to prevent biliary obstruction and cholangitis, which can be fatal. This is usually achieved endoscopically by performing endoscopic retrograde cholangiopancreatography (ERCP) or through surgical common bile duct (CBD) exploration.

Sickle cell cholangiopathy

Sickle cell cholangiopathy is a form of ischemic cholangiopathy which may be encountered in patients with SCD. While hyperbilirubinemia can be multifactorial in these patients, elevated serum bilirubin with abnormal biliary imaging findings should point towards possible evaluation for Sickle cell cholangiopathy.

Pathophysiology: The underlying mechanism of sickle cell cholangiopathy is ischemic injury to the biliary tree due to recurrent sickle cell crisis affecting end arteries of the biliary tree ultimately causing hypoxic injury[43,44]. While initially this can lead to dilation of biliary ductal system, recurrent insult can result in strictures in extrahepatic and intrahepatic biliary ducts. Biopsy is often not necessary and if obtained, mostly shows cholestasis. Occasionally findings of ischemia such as ischemic bile duct necrosis, biliary fibrosis can be observed

Biochemical abnormalities: Most patients with have elevated bilirubin mainly direct bilirubinemia, elevated alkaline phosphatase and variable elevations of transaminases.

Clinical feature: In early stages, most patients present with cholestatic jaundice. In a study done on 224 SCD patients with cholestatic jaundice receiving total of 242 ERCP, prevalence of dilated biliary ducts was 24.6%[45]. Common causes of biliary obstruction such as stones, mass have to be excluded prior to attributing these changes to cholangiopathy. As the disease progresses to development of biliary strictures, patients might present with symptoms of obstructive jaundice such as pruritus, dark urine, clay colored stool and jaundice. These patients can also develop ascending cholangitis. Chronic liver failure/cirrhosis may also occur in advanced stages of disease.

Treatment: Patient who are asymptomatic but are found to be having dilated biliary ducts, should be closely followed up since they are at a high risk of having bile duct stones[45]. Endoscopic therapy is the mainstay for patients with choledocholithiasis or biliary strictures. The role of liver transplantation for patients with recurrent cholangitis or cirrhosis in patients with sickle cell cholangiopathy remains controversial.

LIVER TRANSPLANTATION IN SCD

Data regarding liver transplant in Sickle cell hepatopathy is limited. Although it has been proposed on a case by case basis, only a few case series with a total of 18 cases where Orthotopic Liver Transplant (OLT) was performed have been reported (Table 3). With more recent advances in transplant management as well as advanced understanding in the disease process of sickle cell hepatopathy, this field appears to have fair potential to be a viable treatment option in SCH as is suggested by the most recent case series reported by Hurtova *et al*[46]. In this cohort, the liver transplant was performed with selective inclusion criteria as well as strict post-transplant adherence to exchange transfusion protocol at least for first 6 mo to keep HbS < 30% and Hb between 8-10 g/dL. Patients with significant cardiovascular and respiratory co-morbidities were excluded from the trial. The 3 year survival rate close to 67% and 10 year survival rate close to 44% were observed in this study suggesting that although liver transplant does not affect the disease course in SCD, it has potential to improve at least short term and survival rate in this patient population. A common observation among all these liver transplant patients was that efforts to maintain HbS < 25%-30% were associated with improved post-transplant survival[47]. It should be kept in mind that OLT is not a benign treatment and even post-transplant liver grafts are at increased risk of vascular thrombosis and graft failure as well as risk of infection due to multiple exchange transfusions. Moreover, sickle cell hepatopathy, hepatitis C and

transfusion related iron overload can also develop in the transplanted liver.

CONCLUSION

Sickle cell hepatopathy is a spectrum of disease manifestations with varying levels of severity due acute or chronic changes within the hepatobiliary system in patients with sickle cell hemoglobinopathy. With better understanding of disease pathophysiology, advances in treatment options and improvement in the care of SCD patients, the overall survival of patients with SCD has improved significantly. This paper highlights the pathophysiology of the hepatobiliary manifestations of sickle cell disease, discusses clinical presentation and biochemical features to help identify and manage the appropriate manifestations along this disease spectrum.

This review also raises certain important un-answered questions which need to be further studied. Data to identify risk factors for developing acute hepatopathy is lacking. Treatment for most acute hepatopathy manifestations still remains mainly supportive and the role of hydroxyurea and other anti-sickling agents in preventing the hepatobiliary manifestations has not been defined. The role of liver transplantation, though offered at some centers, still remains controversial and the need for prophylactic cholecystectomy is still questionable. Finally, about 10% SCD patients are found to have cirrhosis on autopsy which cannot be explained by any other etiology and it is yet unclear as to what increases this risk to progression towards cirrhosis.

Research of these unanswered questions can potentially lead to better management of these patients and alter the natural history of disease possibly reducing the morbidity and mortality associated with end stage liver disease in SCD.

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