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Spectrum of liver affection in children with sickle cell disease: case series

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Abstract

Background Sickle cell hepatopathy (SCH) is a relatively uncommon complication of sickle cell disease (SCD), yet it does not accommodate variations in presentation, outcome, or severity according to age.

Aim To present SCH characteristics and assess the effect of implementation of a high-suspicion systematic diagnostic approach and early intervention plan of management.

Methods This case series presented the characteristics of five children with SCD with variable hepatic manifestation and implemented a diagnostic approach that included testing the transaminases and bilirubin in any patient with any suspicion of liver affection.

Results The five patients had a complicated SCD history. They all presented with fever, abdominal pain, and deepening of jaundice. The final diagnosis was reached with a more individualized approach; two had significant coagulopathy and were diagnosed with sickle cell intrahepatic cholestasis, while one had normal synthetic functions of the liver with rising transaminases and bilirubin levels, as well as high titer of Epstein–Barr virus diagnosed as acute viral hepatitis complicated with sickle cell hepatic crisis. One other patient had markedly elevated bilirubin with mild elevation of transaminases, and magnetic resonance cholangiopancreatography showed acute extrahepatic biliary dilatation treated by endoscopic removal of the stone. The fifth patient proved to have portal vein thrombosis by portal duplex causing portal hypertension and decompensated liver. The management plan included early exchange transfusion to keep their hemoglobin S (HbS) below 15% which was performed in three of the patients, in addition to aggressive supportive measures for correction of coagulopathy with full recovery and normalization of their liver functions.

Conclusion Despite the diagnostic challenges, the lack of standard diagnostic criteria, and the overlapping clinical presentation of SCH, the management and outcomes improved by following a systematic diagnostic approach.

Keyword Sickle cell hepatopathy, Sickle cell disease, Children, Case series

Introduction

Sickle cell disease (SCD) is an inherited group of hemoglobin disorders that include homozygous sickle cell anemia (SS), sickle cell/hemoglobin C (SC) sickle/β thalassemia (SB), and other compound heterozygous conditions [1]. SCD represents a chronic, debilitating medical condition that affects patients across their lifespan [2] and is associated with lifelong debilitating multisystem organ damage, including the liver, and is responsible for the continued high morbidity and mortality associated with the disease [3].

Liver disease in patients with SCD can result from the effects of sickling of erythrocytes within the vasculature of the liver with consequent hypoxic liver injury; complications related to the multiple blood transfusions some patients require, including viral hepatitis and iron overload; gallstones with biliary obstruction; or coincidental liver pathology [4]. The clinical spectrum of liver disease

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encountered includes mild abnormalities of liver function in asymptomatic patients to dramatic acute clinical crises associated with an acute liver failure phenotype to cirrhosis [5].

Sickle cell hepatopathy (SCH) is a broad term encompassing the range of liver diseases [5] arising from a wide variety of insults to the liver in patients with SCD; it is a relatively uncommon complication that occurs predominantly in patients with homozygous sickle cell anemia and to a lesser extent in patients with sickle cell trait, hemoglobin SC disease, and hemoglobin S β thalassemia [6]. SCH also known as intrahepatic cholestasis is a clinical syndrome characterized by marked hyperbilirubinemia and variable clinical presentations and outcomes [7]. SCH is an all-encompassing term that includes acute processes related to sickling causing an acute hepatic crisis, acute intrahepatic cholestasis, acute hepatic sequestration, and chronic liver disease, including chronic cholestasis, as well as complications of multiple transfusions including viral hepatitis and iron overload [8].

SCH can be seen in about 10% of patients with SCD, with abnormal liver function tests in one-third, hepatomegaly noted in 91% of autopsies of those with SCD, and cirrhosis noted in 16 to 29% of autopsies. In children, severe liver disease is rarely reported because of misinterpretation of liver tests and possible confusion between hemolysis and liver disease markers. Hence, it might be underdiagnosed and insufficiently treated. Large series are rare, reporting mild elevation of transaminases and cholelithiasis as the main hepatobiliary abnormalities [9]. We present SCH characteristics and highlight the effect of implementation of a high-suspicion systematic diagnostic approach and early intervention plan of management.

Methods

This case series highlights the characteristics of five children with SCD presented with variable hepatic manifestations. The study was approved by the research ethical committee center in Ain Shams University hospitals on 14th July 2024 under the registration number FMASU R159/2024. The patients were diagnosed and followed up prospectively at the Pediatric Hematology Oncology and BMT Department, Ain Shams University, Cairo, Egypt. An informed consent was obtained from all legal guardians of the participants, and an assent form was obtained from the participant whenever applicable. All procedures were performed after fulfilling the ethical standards of the Institutional Research Committee per the Helsinki Declaration 2013.

The clinical characteristics

All the participants were thoroughly evaluated with special emphasis on abdominal, neurological, and cardiac examination and SCD-related complications. Their demographic and clinical characteristics are illustrated in Table 1.

The laboratory analysis

Data was collected from the electronic medical records including complete blood count (CBC) using Sysmex XT-1800i (Sysmex, Kobe, Japan) and hemoglobin electrophoresis analysis by HPLC using D-10 (Bio-Rad, Marnes-la-Coquette, France). The diagnostic approach to start

Table 1 Demographic and clinical characteristics of the studied patients with sickle cell disease

Variable	Case 1	Case 2	Case 3	Case 4	Case 5
Demographic characteristics					
Age (year)	7	5	7	15	11
Sex	Male	Female	Male	Female	Female
Order of birth	1	2	1	1	3
Consanguineous parents	Positive	Positive	Positive	Positive	Positive
Family history	Positive	Positive	Positive	Positive	Positive
Clinical characteristics					
Age of diagnosis (month)	9	9	6	12	12
Hemoglobin electrophoresis					
HbS%	81.7	93.7	78.6	59.5	65.5
HbA%	0	0	0	0	0
HbA2%	3.1	3.2	3.4	3.2	2.5
HbF%	15	3.1	18	37.3	32
Genotype	Not done	Done	Not done	Not done	Not done
Sickle subtype	$S\beta^0$	SS	$S\beta^0$	$S\beta^0$	$S\beta^0$

HbS hemoglobin S, *HbA* hemoglobin A, *Hb A2* hemoglobin A2, *HbF* hemoglobin F, *SS* sickle cell anemia, SB^0 sickle/$^{\beta 0}$ thalassemia

with alanine aminotransferase (ALT), aspartate transferase (AST), total serum, and indirect bilirubin using Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany) prothrombin time (PT) and partial thromboplastin time (PTT).

Imaging

Pelviabdominal ultrasound with a portal and mesenteric duplex and cholangiopancreatography (if needed) were performed to assess the liver, spleen, and intra- and extrahepatic biliary tract.

A stepwise approach for suspected cases of sickle cell hepatopathy, who presented clinically with right upper quadrant abdominal pain and deepening of jaundice, was implemented as illustrated in Table 2.

The management plan

It includes early exchange transfusion to keep their Hb S below 15% when indicated, in addition to aggressive supportive measures for correction of coagulopathy with an attempt for full recovery and normalization of their liver functions.

Case 1

A sickle thalassemia ($S\beta^0$) patient, who was not compliant with hydroxyurea (HU), had a complicated history which included recurrent hospital admission with painful vaso-occlusive crisis (VOCs), two attacks of bilateral septic ankle arthritis requiring surgical drainage, and debridement with systemic antibiotics at the age of 2 and 8 years. He also had one attack of acute chest syndrome (ASC) and repeated attacks of hemolytic crisis necessitating simple blood transfusion complicated with secondary iron overload in the form of a high ferritin level of 2219 ng/dl requiring deferasirox on 15 mg/kg/day. His liver, kidney functions, and transcranial Doppler velocity were normal on regular follow-up visits.

He presented with a disturbed consciousness level, fever, vomiting, right upper quadrant abdominal pain, darkening of urine with deepening of jaundice, and tachypnea. Initial workup for suspected SCH was performed and revealed elevated transaminases tenfold with direct hyperbilirubinemia and derangement of kidney functions with an abnormal bleeding profile. His venous blood gases showed metabolic acidosis with a positive anion gap and serum ammonia of 113 µmol/l. His HbS fraction was 32.4%, while C-reactive protein, electrolytes, and hepatitis B and C viral markers were normal. Pelviabdominal ultrasound with mesenteric duplex showed multiple gall bladder stones; however, his brain computerized topography was normal.

Supportive treatment was initially started in the form of fresh-frozen plasma transfusion, intravenous fluids, and antibiotics with simple packed red blood cell transfusion to avoid the hazardous exchange transfusion as the bleeding profile is still not corrected. Unfortunately, the patient's condition deteriorated, and he developed progressive respiratory distress, dropping platelet count reaching 12,000/µl with pulmonary hemorrhage requiring intubation. His chest X-ray showed bilateral lung infiltrates as in Fig. 1A. The patient received recombinant factor VII, fresh-frozen plasma, platelet transfusion to control the bleeding, upgrading his antibiotics, administering steroids on 2 mg per kg, and launching an exchange transfusion. The patient was extubated after 2 days of being intubated. One day later, the patient developed focal convulsions on his left arm. His magnetic resonance imaging, venography, and arteriography showed pictures of posterior reversible encephalopathy syndrome which could be attributed to hypertension. The patient started captopril and continued his supportive measures, together with an exchange transfusion with a gradually increasing volume for four consecutive days. The patient's general condition improved with a regain of full consciousness level and gradual improvement of his chest X-ray as in Fig. 1B and laboratory parameters with total bilirubin reaching 4.4 mg/day, direct bilirubin 2.1 mg/dl, and his last hemoglobin electrophoresis with HbS fraction of 4%. He had an attack of recurrent SCH and kept on regular monthly exchange transfusion owing to the life-threatening complication he had. Upon his annual assessment, he was maintained on regular exchange transfusion and had no further attacks.

Case 2

A girl with SS genotype whose past medical history revealed recurrent hospital admission with painful VOCs, one attack of pneumonia, and correction of her cleft palate at the age of 2 years. She presented with fever, right upper quadrant abdominal pain, and deepening of her jaundice. Liver function showed elevated transaminases twofold with direct hyperbilirubinemia, normal kidney function, bleeding profile, HbS fraction of 35.5%, and serum ammonia of 64 µmol/l. The C-reactive protein was mildly elevated, and electrolytes and hepatitis B and C viral markers were normal. She had lymphocytosis with atypical lymphocytes on her blood film, Epstein-Barr virus (EBV) IgM was requested and tested positive, and EBV polymerase chain reaction (PCR) was 8836 copies/ml. Pelviabdominal ultrasound with mesenteric duplex showed hepatomegaly. The magnetic resonance cholangiopancreatography (MRCP) showed no intrahepatic nor extrahepatic biliary dilatation with gall bladder and periportal edema. The patient was diagnosed with acute sickle cell hepatic crisis. She received supportive treatment with antibiotics and exchange transfusion keeping her HbS less

Table 2 Stepwise approach for suspected cases of sickle cell hepatopathy

Variable	Case 1	Case 2	Case 3	Case4	Case5
Clinical presentation					
Right upper quadrant pain	Positive	Positive	Positive	Positive	Positive
Deepening of jaundice	Positive	Positive	Positive	Positive	Positive
Suspected sickle cell hepatopathy					
First step: lab assessment					
Alanine aminotransferase; IU/L	481	85	380	100	14
Aspartate aminotransferase; IU/L	308	81	338	95	19
Total bilirubin; mg/dl	7.9	18	10	41.6	2.5
Direct bilirubin; mg/dl	4.8	9	8.7	19.9	1
Prothrombin time; s	57.1	19.8	20	16.1	12.5
Partial thromboplastin time	>60	47	47	36	36.6
Total leukocyte count 10^3/µl	15.6	20.1	24.5	20.3	4.7
Neutrophile count 10^3/µl	7.35	6.3	10.5	14.3	2.13
Lymphocyte count 10^3/µl	1.6	12.5	2.5	4.3	1.84
Hemoglobin g/dl	8.8	9.2	5.7	8.1	12.2
Platelet count 10^3/µl	432	241	191	693	105
Serum creatinine mg/dl	1.1	0.3	0.4	0.4	0.3
Urea mg/dl	14	7	7	14	15
Alkaline phosphatase IU/L	497	196	239	239	41
Albumin g/dl	4.3	2.3	2.8	4.1	4.1
Second step: radiological assessment					
Abdominal US with mesenteric duplex	Multiple gall bladder stones with no intra- nor extrahepatic biliary dilatation	Hepatomegaly	Hepatosplenomegaly with no intrahepatic nor extrahepatic dilatation	Obstructive cholangiopathy	Portal vein thrombosis with portal hypertension
Third step					
C-reactive protein	1.5	105	170	10.3	2.5
Hepatitis C virus antibody	Normal	Normal	Normal	Normal	Normal
Hepatitis B virus antigen	Normal	Normal	Normal	Normal	Normal
Hemoglobin S% at the time of presentation	32.4	35	80	46	60
Final diagnosis					
Diagnosis	Acute sickle cell intrahepatic cholestasis	Acute Epstein–Barr viral hepatitis complicated with sickle cell hepatic crisis	Acute sickle cell intrahepatic cholestasis	Obstructive cholangiopathy	Portal vein thrombosis with portal hypertension

than 15% with gradual improvement of her clinical condition and her labs with gradual normalizing of her bilirubin level. Upon her regular follow-up, she did not suffer from any clinical pattern of SCH since then, and her EBV PCR was repeated and was undetectable (Fig. 2).

Case 3

A sickle thalassemia ($S\beta^0$) Nigerian boy with a past medical history showing recurrent hospital admission with painful crises and acute ischemic stroke at the age of 5 years. The patient was on a stable dose of hydroxyurea

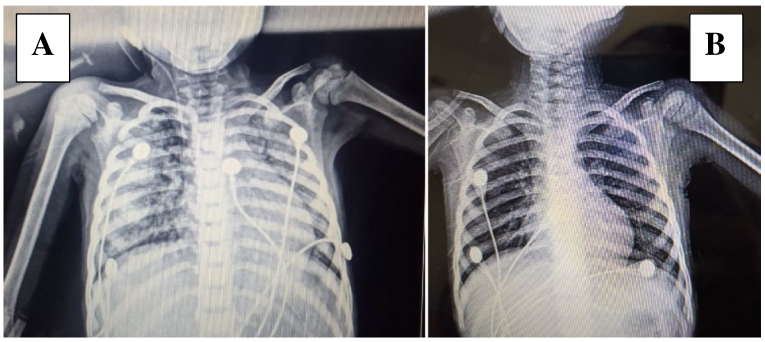

Fig. 1 Chest X-ray of case 1. **A** Initial chest X-ray showed bilateral lung infiltrates. **B** Follow-up chest X-ray showed improvement

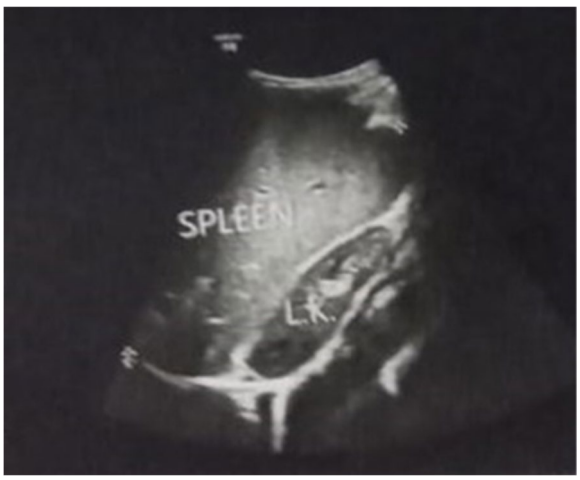

Fig. 2 Abdominal ultrasound of case 2. Abdominal ultrasound shows splenomegaly

at 30 mg/kg and exchange transfusion; however, he was not compliant. His liver and kidney functions were normal on a follow-up visit.

He presented with low-grade fever, vomiting, generalized bony aches, generalized abdominal pain, and darkening of urine with jaundice. Transaminases were normal with mild elevation of unconjugated bilirubin. He was treated as a case of an acute painful crisis with intravenous fluids, antibiotics, and analgesics, and then on day 4 of admission, the patient developed high-grade fever (39 °C), with dropping of platelet count and hemoglobin drop, upon which packed red blood cells (PRBCs) transfusion was given. This was associated with right upper quadrant pain, deepening of jaundice, tachypnea, and acute deterioration in liver functions with an elevation of conjugated bilirubin and 8- to ninefold increase in transaminase, HbS fraction was 75%, ammonia level was 50 µmol/l, and C-reactive protein was170 mg/dl, whereas electrolytes and hepatitis B and C viral markers were normal. Pelvi-abdominal ultrasound with mesenteric duplex showed hepatosplenomegaly. He was diagnosed with acute sickle cell intrahepatic cholestasis and transferred to the pediatric intensive care unit (PICU) to receive supportive treatment with exchange transfusion keeping his HbS less than 15% and correction of coagulopathy with fresh-frozen plasma with gradual improvement of his clinical condition and his labs with gradual normalizing of his bilirubin level until normalization. Owing to the life-threatening presentation of the patient, he was kept on regular exchange transfusion with no further attacks of SCH, and he was maintained on quarterly assessment of his liver function tests.

Case 4

A girl with sickle thalassemia ($S\beta^0$) whose past medical history included recurrent hospital admissions with painful and hemolytic crises. She presented with acute right upper quadrant abdominal pain, deep jaundice, and febrile. Her liver function showed hyperbilirubinemia predominantly conjugated, mildly elevated transaminases, and a HbS fraction of 46%. The C-reactive protein was mildly elevated at 10.5 mg/dl, while electrolytes and hepatitis B and C viral markers were normal. Pelviabdominal ultrasound with mesenteric duplex showed a common bile duct stone of 6 mm with obstructive cholangiopathy. She underwent endoscopic retrograde cholangiopancreatography (ERCP) showing three large stones with intrahepatic biliary radicle dilatation. Sphincterotomy and sphincteroplasty were done using 12-mm balloon dilation, and another stone could not be removed with the insertion of 10-French 100-mm stent. The patient had a marked drop in bilirubin level 19.5 mg/dL (conjugated = 8.7 mg/dl).

Case 5

A girl with sickle thalassemia ($S\beta^0$) whose past medical history revealed common complications of SCD in the form of recurrent hospital admission with painful VOCs,

fracture of her tibia with cast at the age of 3 years, and recurrent hospital admission with wheezy chest. The patient presented at the age of 5 years with progressive abdominal distension, and her clinical examination revealed an enlarging splenomegaly with no palpable hepatomegaly. Liver function tests showed mild hyperbilirubinemia predominantly conjugated (1 mg/dl) with normal transaminases, and her complete blood picture showed a low platelet count with normal hepatitis B and C viral markers. Pelviabdominal ultrasound with mesenteric duplex showed portal vein thrombosis with portal hypertension. Upper gastro-esophagoscopy showed esophageal varices, and she electively underwent injection sclerotherapy. Her serial complete blood picture showed a falling platelet count reaching 50×10^3/μl. She was on supportive treatment with regular endoscopy and close follow-up of her hydroxyurea dose for fear of further platelet drop and regular liver function tests.

Discussion

The clinical manifestations of SCH vary depending on the relative degrees of cell trapping, ischemia, and intracanalicular cholestasis. There is an overlap among these entities; hence, precise classification is often challenging [9]. Despite several studies addressing SCH in adults, few are presented in the pediatric age group. Here, we discussed five patients: four patients presented with acute hepatobiliary affection, and one had chronic liver affection. Although previously reported that children may present with a milder form of sickle hepatopathy than adults [10], the two patients who had a severe form in our cohort were aged 7 years old.

SCH is described as obstructive jaundice, in contrast to jaundice due to hemolysis, with two different clinical outcomes: the mild self-limited type with a serum total bilirubin level in the 10–30 mg/dl range and the severe type with a bilirubin level greater than 30 mg/dl [11]. In this study, we implemented an institutional systematic approach for early diagnosis made of proper and accurate clinical assessment for those presented with localized upper quadrant abdominal pain or any suspicious liver affection, followed by the full liver profile assessment, including the synthetic function of the liver and exclusion of acute viral hepatitis together with hematological assessment by complete blood picture and hemoglobin electrophoresis. Initial imaging by pelviabdominal ultrasound with a portal and mesenteric duplex is to be performed and if needed proceed to cholangiopancreatography. This approach allowed timely diagnosis and, hence, rapid intervention.

Digging deep into the clinical characteristics and risk factors that may precipitate liver complications in SCD, it was found that two of the three patients who presented with acute liver affection had acute intrahepatic cholestasis. All had the more severe phenotype of SCD SS or $S\beta^0$, according to their hemoglobin electrophoresis, and were previously manifested with multiple sickle cell-related complications, which may go with their uncontrolled disease. Although two of them had HbS levels around 30%, they presented with severe acute complications, which confirms what was previously reported that a lower level of HbS% is not always protective [9].

Sickle hepatopathy can arise spontaneously or be triggered by infection or autoimmune diseases [12]. The acute presentation of one of the patients was triggered by acute EBV infection, as evidenced by atypical lymphocytosis and positive EBV IgM and PCR. There are few prior reports of EBV-induced sickle hepatopathy in individuals with SCD, as Towerman and his colleagues reported similar cases of EBV-induced sickle cell hepatopathy and recommended testing for EBV infection in SCD patients presenting with acute sickle hepatopathy. This may predict a good prognosis with supportive measures corresponding with what happened to our patient [12].

The frequency of cholelithiasis in patients with SCD is variable, ranging from 4 to 55%, and increasing with age. The ERCP provides therapeutic interventions, including endoscopic sphincterotomy and stone extraction, dilatation of strictures, and placement of stents and biliary drainage catheters [13]. Following the systematic approach also helped us in the early diagnosis of one of our patients with obstructive cholelithiasis complicated by cholangiopathy. The patient performed an early stone removal and stent insertion by ERCP, which resulted in a rapid drop in her bilirubin level.

Treatment of acute sickle cell hepatic crisis is mainly supportive, including intravenous fluids and oxygenation. In severe cases, patients may require an exchange transfusion, wherein the patient's blood is replaced with the donor's blood; this is very effective in lowering the level of HbS below 30% of the total hemoglobin without raising the total hemoglobin level above 10 g/dL [14].

Hydroxyurea, on the other hand, has not been well explored in the context of SCH. While it can be extrapolated that the exact mechanisms responsible for reduced VOCs and ACS and decreased transcranial Doppler measurements, among other complications, would also decrease the incidence of sickle cell hepatopathy, no studies have been carried out to confirm this hypothesis. However, effects of hydroxyurea like induction of hemoglobin F reduce the propensity of red blood cells

to undergo sickling in the low oxygen tension environment within hepatic sinusoids, Moreover, the resultant decrease in the hemolysis rate diminishes the bilirubin load that contributes to intrahepatic cholestasis [15]. Consequently, in our practice, we ensure that patients receive the maximum tolerated dose of hydroxyurea.

In our patients, the plan of treatment for acute hepatic sickle cell crisis included the early start of exchange blood transfusion (EBT). EBT is widely used in acute liver syndromes and chronic liver disease, and reaching such low levels of HbS (< 15%) was the key to success in the three cases presented with acute hepatic sickle cell crisis. This approach was previously adopted in the management of cerebrovascular diseases in SCD [14].

Monitoring children with SCD for hepatopathy is recommended, with yearly monitoring of liver enzymes, gamma GT, and alkaline phosphatase. If serum ALT > 2 × upper limit of normal (ULN) and/or gamma-glutamyl transferase (γ-GT) 1·5–2 × ULN, they should be investigated from a liver disease perspective. Abdominal US should be performed yearly after 5 years of age. Serum ferritin should be monitored annually in children with a history of transfusion and monthly in case of chronic transfusion. Liver MRI is recommended annually for evaluating iron burden in patients receiving more than 10 transfusions per year or with a ferritin > 1000 µg/L. Liver biopsy in patients with SCD is indicated for the investigation of persistently abnormal liver function tests (LFTs) to rule out coexisting pathology [15].

There is not enough evidence on how to identify patients at risk of developing chronic liver disease and which interventions are best to prevent further disease progression. Interventions such as hydroxyurea in those with multiple vaso-occlusive crises, exchange transfusions to keep HbS levels below 30%, and ursodeoxycholic acid can be considered, as they have shown some benefits [16]. That is why in patients with recurrent SCH or life-threatening presentation, we advocated the strategy of prophylactic exchange transfusion.

Clinical trials investigating the usefulness of early cholecystectomy and the role of hydroxyurea in preventing SCD hepatopathy, as an endpoint, are required [17]. Liver transplantation (LT) should be considered for very selected patients at centers that are experts at managing LT and SCD [18]. HSCT with an available suitable donor would be curative for SCD and would avoid the risk of recurrence of SCH in the donor's liver. This could be an option while evolving therapies become a reality.

One of the limitations of our study is the relatively small sample size; however, an institution registry was planned and approved by EC under number FMASU: POS/2024 and implemented which will allow for a larger sample size in the near future.

Conclusions

Although the clinical presentation of sickle cell hepatopathy may overlap, following a systematic diagnostics approach improved management and outcomes. Early exchange transfusion to keep HbS less than 15% improved survival in our patients presenting with life-threatening sickle cell intrahepatic cholestasis.

Abbreviations

SCH	Sickle cell hepatopathy
SCD	Sickle cell disease
HbS	Hemoglobin S
SS	Sickle cell anemia
SC	Sickle cell/hemoglobin C
SB	Sickle/β thalassemia
VOCs	Vaso-occlusive crisis
MRCP	Magnetic resonance cholangiopancreatography

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The authors have no disclosures to declare, and the manuscript has not been published previously.

Authors' contributions

The corresponding author, on behalf of all authors, hereby states that all authors have contributed significantly to the manuscript and have reviewed and agreed upon its content. A ll authors were involved in the concept, design, data collection, analysis, and drafting of the manuscript.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Regulatory Board of Pediatrics Department, Faculty of Medicine, Ain Shams University, as well as the Research Ethics Committee, Faculty of Medicine, Ain Shams University on 14th July 2024 under the registration number FMASU R159/2024 with Assurance No. FWA00017585. This is a retrospective cohort study; informed consent was obtained whenever applicable.

Consent for publication

We did not include any identifying images or other personal details of participants that may compromise anonymity.

Competing interests

The authors declare that they have no competing interests.

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