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Paediatric sickle cell disease presenting with hepatobiliary symptoms—a case presentation and brief literature review

Aditi Kumar[1*], Rashmi Ranjan Behera[1], Samarendra Mahapatro[1], Ranjan Patel[2], Hemanta Nayak[3] and Amit Kumar Satapathy[1]

Abstract

Background Sickle hepatopathy is the hepatobiliary dysfunction associated with sickle cell disease. It has a varied spectrum ranging from asymptomatic transaminasemia to gallstones or fulminant liver failure. Hepatobiliary manifestations may be the initial presentation in children with undiagnosed sickle cell disease as seen in our three index cases. This may mimic a primary liver disease, delaying definite diagnosis and management.

Case presentation We describe three cases. The first case was a 9-year-old girl child with cholecystitis with choledocholithiasis, the second case was a 15-year-old boy with acute hepatitis of unidentified aetiology, and the third case was a 3-month-old infant with neonatal cholestasis in absence of common structural or metabolic cause. All three cases had underlying haemolytic anaemia with splenomegaly and belonged to the sickle belt of the region. The final diagnosis in all three index cases was sickle cell disease with hepatopathy.

Conclusion The clinical syndrome of hepatitis or cholestasis with or without cholangitis in the background of splenomegaly and haemolytic anaemia should prompt screening for sickle cell disease.

Keywords Sickle cell hepatopathy, Choledocholithiasis, Acute sickle intrahepatic cholestasis, Acute hepatic sickle crisis, Sickle cell cholangiopathy, Case report

Background

Sickle cell disease (SCD) or homozygous sickle cell anaemia is an autosomal recessive haemoglobinopathy characterized by pathological haemoglobin S (HbSS). Among South Asian nations, India has the highest prevalence of SCD [1]. A spatial epidemiological study by Hockham et al. showed the highest predicted frequency of the sickle cell allele occurred in up to about 10% population of central India extending from south-eastern Gujarat to south-western Odisha [2]. The hallmark pathophysiology in SCD is the hypoxemia-induced polymerization of HbSS containing red blood cells, leading to intravascular sickling, vaso-occlusive crisis, and ischemic damage to the affected organ. SCD leads to a chronic debilitating illness with multiorgan involvement of variable severity, with mortality as high as 50–80% in under five children with SCD in resource-limited nations [1, 3].

Sickle cell hepatopathy (SCH) is a spectrum of hepatobiliary manifestations in SCD patients. The presentations range from asymptomatic mild transaminasemia to overt liver failure secondary to the intrahepatic cholestatic sickle crisis. The incidence of SCH is as high as 37% in children with sickle cell disease, gallstones being the most common manifestation [4]. There are recommendations

*Correspondence:
Aditi Kumar
ped_aditi@aiimsbhubaneswar.edu.in
[1] Department of Pediatrics, All India Institute of Medical Sciences (AIIMS) Bhubaneswar, Bhubaneswar, India
[2] Department of Radiodiagnosis, AIIMS Bhubaneswar, Bhubaneswar, India
[3] Department of Gastroenterology, AIIMS Bhubaneswar, Bhubaneswar, India

for early screening and management guidelines for SCH to improve the outcomes of such patients [5]. However, in the absence of universal screening for SCD, the initial age and presentation remain uncertain, and SCH may manifest as the first symptom of SCD. In this review, we will detail three paediatric cases presenting with a hepatobiliary complaint mimicking a primary liver disease and were diagnosed with sickle cell anaemia with hepatopathy.

Case presentation

Case 1

A 9-year-old girl child belonging to the Kalahandi district of Odisha State presented with complaints of recurrent abdominal pain for 2 months. The pain had worsened in the last 2 weeks. The child was haemodynamically stable on clinical evaluation with epigastric tenderness, pallor, and mild icterus with firm spleno-hepatomegaly. Ultrasound of the abdomen with Doppler revealed a partially distended gall bladder with few calculi noted in the gall bladder neck region (largest 1.3 cm). There was common bile duct dilatation of 13 mm with distal CBD showing a calculus of 7–9 mm, including mild central intrahepatic biliary radicle dilatation with an enlarged spleen, which was confirmed on magnetic resonance cholangiopancreatography (MRCP). A diagnosis of cholelithiasis with choledocholithiasis was made. Laboratory findings revealed moderate anaemia (Hb 7.7 gm/dL) with reticulocytosis. Liver function showed mild conjugated hyperbilirubinemia (total bilirubin 2.4 mg/dL) with mild transaminasemia (80/42 IU/L) with preserved synthetic function (INR 1.28). A cause for underlying haemolysis was sought, and haemoglobin high-performance liquid chromatography (HPLC) showed an elevated HbS fraction of 69%, confirming sickle cell anaemia with migrated cholelithiasis. Endoscopic retrograde cholangiopancreatography (ERCP) was performed; however, because of the presence of stricture, biliary cannulation failed. The child had mild pancreatitis post-procedure, which improved with conservative management. She was discharged with a diagnosis of SCD with cholelithiasis with cholangiopathy and advised for ursodeoxycholic acid. We obtained a paediatric haematology consultation for chelation therapy and paediatric surgery consultation for interval cholecystectomy prior to discharge and were advised to follow up.

Case 2

A 15-year-old male child resident of Rayagada, Odisha, presented with the first episode of jaundice, accompanied by high-coloured urine, abdominal pain, and prodromal symptoms of 2 weeks' duration. However, there was no history of pale stools, pruritus, or other cholestatic features. The child had a history of red blood cell transfusion 6 months before at a local hospital. There was a history of the father's death because of alcohol-related liver disease. Clinical examination revealed icterus, pallor tender hepatomegaly with firm splenomegaly. The initial clinical suspicion inclined towards acute hepatitis with an infective aetiology with underlying haemolytic anaemia. Other considerations included were primary liver diseases such as Wilson's disease with intravascular haemolysis or autoimmune liver disease with Coomb's positive haemolysis. Laboratory results indicated moderate anaemia (Hb 6.1 mg/dL), cholestatic jaundice (total bilirubin 7.5 mg/dL), elevated transaminase levels (239/190 IU/L), and vitamin K-correctable coagulopathy (2.3→1.24). Viral panels, including hepatitis A, E, and B, came negative. Glucose 6 phosphate dehydrogenase (G6PD) levels were normal, the Direct Coombs Test came negative, and there was no evidence of intravascular haemolysis. Serum ceruloplasmin levels were in normal range, and autoimmune markers were negative. Hb HPLC showed a high HbS fraction of 51%, indicative of homozygous sickle cell disease. Abdominal sonography with Doppler revealed hepatosplenomegaly with right lobe atrophy, altered hepatic echotexture, and a normal biliary tract, portal veins, and hepatic veins. A final diagnosis of SCD with a mild acute sickle hepatic crisis was made. The child was managed with supportive care, and the symptoms improved. The child is on hydroxyurea supplementation, received pneumococcal vaccination, and is in follow-up under paediatric haematology.

Case 3

A 3-month-old male infant from Berhampur presented with jaundice of 1 month accompanied by intermittent pale stools. The child, born of a third-degree consanguineous marriage, had a history of neonatal hyperbilirubinemia requiring 48 h of phototherapy. There was significant pallor, mild jaundice, and diaper staining of urine with pale stools with hepatosplenomegaly. An infantile cholestasis with elevated GGT (299) was initially considered. Biliary atresia seemed less likely due to a well-sized gall bladder (23 mm) with good contractility on sonography and excretory hepatobiliary iminodiacetic acid (HIDA) scan. Furthermore, there was absence of sludge or stones in the biliary tract. However, the presence of significant anaemia (Hb 4.2 mg/dL), leucocytosis (TLC 31,410/mm^3), high reticulocytosis (4.2%), elongated RBCs, and target cells and mixed hyperbilirubinemia (total/direct bilirubin 19/6.7) prompted a comprehensive evaluation for underlying haemolysis. Other supportive investigations revealed high LDH (584 IU/L), with hyperferritinemia (2770 ng/ml). G6PD levels and the Direct Coombs test returned negative. Screening for genetic/metabolic

causes of cholestasis revealed normal coagulogram (INR 1.3), serum lactate (2.1), creatinine kinase levels (95 IU/L), and mildly elevated alphafetoprotein values (1210 IU) with normal eye, spine, and cardiac evaluation for Alagille's syndrome. Sepsis screen was negative (CRP 3.98 mg/L) with negative blood and urine culture and normal thyroid profile. The Hb HPLC of the infant revealed an HbS percentage of 48%, with parental HPLC showing sickle cell trait confirming SCD in the child. The case was labelled as transient infantile cholestasis associated with SCD. Subsequently, the child required a packed red blood cell transfusion. Supportive care in the form of ursodeoxycholic acid and vitamin supplements was continued and immunization including pneumococcal vaccination and antibiotic prophylaxis was given. The child is in follow-up at Pediatric Hematology OPD. Parents were counselled for genetic testing for disease confirmation and repeat HPLC of the child at 1 year of age.

In all three index cases, parents were carriers and unaffected; however, they resided in the sickle belt of Odisha. The detailed reference of blood investigations is provided in Table 1.

Discussion

Sickle cell disease often presents with mild unconjugated hyperbilirubinemia with isolated elevation of aspartate aminotransferase due to underlying haemolysis and ineffective erythropoiesis. However, conjugated hyperbilirubinemia and elevated alanine aminotransferase are specific to hepatobiliary pathology. These manifestations, ranging from gallstones to fulminant hepatic failure, have been grouped under sickle cell hepatopathy.

Table 1 Laboratory investigations of the three SCH cases at admission

Investigations	Case 1	Case 2	Case 3
Hb (g/L)	7.7	6.1	4.2
TLC (/mm^3)	4130	3100	31,410
Platelet count (/mm^3)	217,000	123,000	239,000
Bilirubin (T/D) (mg/dL)	2.4/2.1	7.5/3.5	19/6.7
AST/ALT (IU/L)	80/42/177	239/190	200/39/1770
ALP/GGT (IU/L)	177/321	296/56	1770/299
Albumin (g/dL)	4.05	3.3	3.2
INR	1.28	1.24	1.32
Creatinine (mg/dL)	0.44	0.38	0.38
Corrected retic count	7.29%	3.54%	4.23%
Sickling test	Positive	-	Positive
S window (HPLC) %	69.2%	51.5%	48%

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyl transpeptidase, *Hb* haemoglobin, *HPLC* high-performance liquid chromatography, *INR* international normalized ratio, *T/C* total/conjugated, *TLC* total leucocyte count

Normal range: Hb = > 11 g/L, TLC = 4000–11000/mm^3, platelet = 150,000–400,000/mm^3, bilirubin = 0.1–1.3 mg/dL, AST = 5–40 IU/L, ALT = 5–40 IU/L, ALP = 35–150 IU/L, GGT = 13–86 IU/L, creatinine = 0.5–1.6 mg/dL

The etiopathogenesis of sickle cell hepatopathy (SCH) is multifactorial. First, this encompasses sickled red blood cells in liver sinusoids or end arteries of bile ducts, resulting in ischemic damage to the centrilobular region of the liver parenchyma or to the bile ducts, respectively. Secondly, it involves iron overload and secondary haemochromatosis or the development of pigment gallstones due to ongoing haemolysis, ineffective haematopoiesis, and repeated blood transfusions. Thirdly, there is a risk of infective hepatitis or transfusion-related infections. Lastly, drug toxicity may occur due to chelation therapy or the trial of alternative medications [6].

The most typical presentation of SCH involves biliary complications that range from gallstones or sludge to cholangiopathy and biliary cirrhosis [7]. Cholelithiasis is the most prevalent SCH, with an overall prevalence of 25% (95% confidence interval 19.4–32%) [8]. These are either detected on USG as a part of regular screening of patients of SCD or may manifest with abdominal pain, as detailed by Soo et al. The most extensive paediatric series reported the detection of cholelithiasis in 58% of SCD (90 out of 156 cases) [4]. These gallstones can migrate and lead to complications like choledocholithiasis, cholangitis, or pancreatitis, presenting with jaundice, fever, and severe pain [9]. While the presentation with a gallstone is not uncommon in SCD, evidence of associated sclerosing cholangitis as the initial presentation of SCD may be rare and can mimic a primary hepatobiliary aetiology [10]. The management involves confirming the migration of stones or cholangiopathy through magnetic resonance cholangiopancreatography (MRCP). Treatment includes supplementation with ursodeoxycholic acid and endoscopic retrograde cholangiopancreatography (ERCP). For symptomatic calculus cholecystitis, laparoscopic cholecystectomy is recommended. Nevertheless, there are no clear recommendations on incidentally detected gallstones [11]. This presentation closely mimics our first case, emphasizing the presentation of SCD with gallstone disease with cholangiopathy.

The hepatic complications of SCH are mild hepatic crisis, moderate sequestration, and fulminant cholestasis. This presentation is similar to our second case, where it presented with right upper quadrant pain, tender hepatomegaly, and jaundice (bilirubin levels within 15 mg/dl) with moderate transaminasemia. In the sizeable single-centre data, the acute hepatic crisis was seen in 27 (4.1%) children with SCH [4]. This crisis was seen in concomitance with other SCD complications in 14/27 (51%). Other manifestations of sickle crisis have been referred to as severe, including hepatic sequestration (moderate crisis) and severe acute sickle intrahepatic cholestatic

disease [11]. Hepatic sequestration results from the active sequestration of sickled RBCs in hepatic sinusoids, causing massive liver enlargement with a concurrent drop in haemoglobin levels. Whereas in the *acute sickle intrahepatic cholestatic variant*, the presentation is severe with marked hyperbilirubinemia (more than 30 mg/dl) and transaminasemia (above 1000 IU/L) with uncorrectable coagulopathy mimicking acute liver failure [7].

The presentation of an acute hepatic sickle crisis in undiagnosed SCD closely mimics acute hepatitis. Conventional workup for acute hepatitis, including viral markers and autoimmune markers, yields negative results in these cases. However, including serum ferritin levels in routine assessments may show elevation. This elevation is often assumed due to hepatic inflammation rather than including SCD in the differential diagnosis. The next step in the workup involves a percutaneous liver biopsy. However, performing a biopsy in SCD-associated hepatic crises is fraught with complications, such as the progression to a severe crisis [12, 13]. There is no specific treatment for SCH, but hydroxyurea, an FDA-approved oral medication for SCD, also works for hepatopathy by halting further progression. In the case of an acute crisis, supportive management is essential, involving blood transfusion or exchange transfusion. The target strategy is maintaining an HbS fraction of less than 20 to 30% [5].

In SCD, newborns have persistent unconjugated hyperbilirubinemia; however, cholestasis is rare. We present our third case with infantile cholestasis. The exact prevalence of transient cholestasis in SCD is unknown. Transient cholestasis may be due to slipped stones, sludge, or inspissated bile; the radiological confirmation may not always be possible. Another possibility is intrahepatic crisis or sepsis which can cause liver dysfunction. The high leucocyte counts as in our case could be due to infections or ongoing haemolysis with nucleated RBCs falsely elevating the leucocyte count. Miller et al. had found the three manifestations of dactylitis, severe anaemia, and leucocytosis in the first 2 years of life to predict the possibility of severe sickle cell disease later in life [14]. The diagnosis in such young infants is challenging because of the persistence of HbF and may require screening HPLC for the carrier status in parents or a genetic study to confirm SCD. Treatment in the form of supportive care results in the resolution of the transient cholestasis. Pneumococcal vaccination and oral antibiotic prophylaxis are given as preventive therapy [4].

While evaluating such cases with cholestatic jaundice and haemolysis, clinicians often face difficulty in diagnosing sickle cell disease-related hepatopathy, especially in the absence of universal birth screening for haemoglobinopathy. In endemic areas with an increased prevalence of SCD, it may not be uncommon for children to present with SCH as their initial manifestation. Clinicians should always maintain a high index of suspicion when a child presents with elevated conjugated bilirubin with haemolysis and consider HPLC testing for haemoglobinopathy/SCD. Early diagnosis will prevent further progression, reducing the risk of severe morbidities and mortality associated with SCH.

Conclusion

The three cases reflect the significance of considering SCD in the differential diagnosis of liver diseases with haemolysis, especially in regions with a high prevalence of SCD. Without universal newborn screening for haemoglobinopathy, SCD can initially present with hepatopathy. The endemicity, family history, and evidence of haemolysis in a jaundiced patient should be strong evidence for a clinician to work up for SCD.

Abbreviations

ERCP	Endoscopic retrograde cholangiopancreatography
G6PD	Glucose 6 phosphate dehydrogenase
Hb-HPLC	Haemoglobin high-performance liquid chromatography
MRCP	Magnetic resonance cholangiopancreatography
SCD	Sickle cell disease
SCH	Sickle cell hepatopathy

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Authors' contributions

AK: designed, drafted, and finalized the manuscript; RRB, RP, SM, HN, AKS: involved in patient care, intellectual inputs, and revision of the manuscript. I will be serving as the corresponding author for this manuscript. All authors have agreed to the by-line order and to the submission of the manuscript in its current form.

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Competing interests

The authors declare that they have no competing interests.

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References

1. Brousse V, Rees DC (2021) Sickle cell disease: more than a century of progress. Where do we stand now? Indian J Med Res 1:4–7

2. Hockham C, Bhatt S, Colah R, Mukherjee MB, Penman BS, Gupta S et al (2018) The spatial epidemiology of sickle-cell anaemia in India. Sci Rep 8(1):17685. https://doi.org/10.1038/s41598-018-36077-w
3. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN (2011) Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med 41(6 Suppl 4):S398-405. https://doi.org/10.1016/j.amepre.2011.09.013
4. Allali S, de Montalembert M, Brousse V, Heilbronner C, Taylor M, Brice J, et al. Hepatobiliary complications in children with sickle cell disease: a retrospective review of medical records from 616 patients. J Clin Med. 2019;8(9). https://doi.org/10.3390/jcm8091481
5. Kyrana E, Rees D, Lacaille F, Fitzpatrick E, Davenport M, Heaton N et al (2021) Clinical management of sickle cell liver disease in children and young adults. Arch Dis Child 106(4):315–320. https://doi.org/10.1136/archdischild-2020-319778
6. Shah R, Taborda C, Chawla S (2017) Acute and chronic hepatobiliary manifestations of sickle cell disease: a review. World J Gastrointest Pathophysiol 8(3):108–116. https://doi.org/10.4291/wjgp.v8.i3.108
7. Theocharidou E, Suddle AR (2019) The liver in sickle cell disease. Clin Liver Dis 23(2):177–189. https://doi.org/10.1016/j.cld.2018.12.002
8. Mohamed SOO, Ibrahim OAO, Mohammad DAA, Ali AHM (2021) Correlates of gallbladder stones among patients with sickle cell disease: a meta-analysis. JGH Open 5(9):997–1003. https://doi.org/10.1002/jgh3.12622
9. Vadlapudi SS, Srivastava A, Rai P, Sing RR, Sarma MS, Poddar U, Yadav RR (2024) Jaundice in a Child with Sickle Cell Anemia: A Case Based Approach. Indian J Pediatric 1:73–80. India: © 2023. The Author(s), under exclusive licence to Dr. K C Chaudhuri Foundation
10. Basit SA, Pokhrel B, Shah SR (2017) Sickle cell hepatopathy masquerading as advance chronic liver disease: 2287. J Am Coll Gastroenterol 11:1253
11. Suddle AR (2019) Management of liver complications in sickle cell disease. Hematology Am Soc Hematol Educ Program 2019(1):345–350. https://doi.org/10.1182/hematology.2019000037
12. Praharaj DL, Anand AC (2021) Sickle hepatopathy. J Clin Exp Hepatol 11(1):82–96. https://doi.org/10.1016/j.jceh.2020.08.003
13. Jitraruch S, Fitzpatrick E, Deheragoda M, Deganello A, Mieli-Vergani G, Height S et al (2017) Autoimmune liver disease in children with sickle cell disease. J Pediatr 189:79-85.e2. https://doi.org/10.1016/j.jpeds.2017.06.035
14. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ et al (2000) Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 342(2):83–89. https://doi.org/10.1056/nejm200001133420203

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