CASE REPORT

Cholelithiasis in sickle cell disease - a case report

Akinbode Saheed Kehinde,[1] Ogundeyi Mojisola Morufat, [1]
Adebola Muktar Babajide,[1] Olanrewaju Moses[2]

Abstract
Sickle cell disease (SCD) is a group of heterogeneous inherited disorders of haemoglobin structure which results in various physiologic derangements and multisystemic complications. An important long-term complication of chronic hemolysis is gallstone formation (cholelithiasis). Symptomatic gall stones may present in the form of acute abdomen or abdominal pain that mimics abdominal vaso-occlusive crisis. Early recognition of vulnerable children with cholelithiasis improves patients' care and reduces morbidities. We report the case of a 14-year-old male sickle cell anaemia patient with acute calculus cholecystitis; to create awareness of the possibilities of symptomatic cholelithiasis which presents like other gastrointestinal and hepatobiliary pathologies in SCD.

Keywords: Sickle cell disease, cholelithiasis, abdominal pain, case report.

Introduction

Sickle cell disease (SCD) is a group of inherited disorders of the red blood cells, characterized by chronic haemolysis, vaso-occlusion and endothelial injury; all of which herald multi-organ dysfunction.[1,2] The most common of the SCD spectrum is sickle cell anaemia (HbSS) which results from the homozygous inheritance of two copies of haemoglobin S (HbS); HbS arises from a single-point mutation on the β-globin gene (HBB) subunit of chromosome 11 that results in replacement of glutamic acid with valine on position 6 of the globin chain.[2,3] Other common types of SCD are heterozygous HbSC and thalassaemias (HbSβ^0 and HbSβ^+). Both homozygous HbSS and HbSβ^0 thalassaemia phenotypes have a more severe clinical course than the others.[2,4] There are more than 300,000 new cases of SCD worldwide, a significant number of whom are borne in sub-Sahara Africa, Middle East and South Asia.[5,6]

In SCD patients, the hepatobiliary system is the most affected within the digestive tract, causing acute hepatic dysfunction and chronic hepatobiliary complications.[4,7,8] Acute hepatic dysfunction in SCD manifests in the form of acute sickle cell hepatic crisis, acute hepatic sequestration, intrahepatic cholestasis, and overt liver failure; all of which are grouped under acute sickle cell hepatopathy, a life-threatening clinical condition.[7,8] The chronic hepatobiliary complications of this condition include transfusion-related iron overload, viral hepatitis and cholelithiasis.[7–9] Similarities exist in the clinical presentation of both acute and chronic entities, hence, there is a need for a high index of suspicion in distinguishing the different conditions.

Cholelithiasis (gall stones) in SCD is connected to increased bilirubin production as a result of chronic hemolysis, yielding radio-opaque substances formed from calcium bilirubinate crystals.[3,6] Cholelithiasis is rare in otherwise healthy children, but common in predisposing conditions such as SCD, obesity, cystic fibrosis and abnormalities of the biliary trees among others.[10,11]

Date Received - 26th January 2024, Date Accepted - 23rd May 2024
Date Published online - 15th August 2024

Corresponding author
Akinbode Saheed Kehinde,
Department of Paediatrics, Federal Medical Center,
Abeokuta, Ogun State, Nigeria.
Email address: saheed.akinbode@npmcn.edu.ng.
Phone No: 08066219618

1.Consultant Pediatrician,
Department of Pediatrics,
Federal Medical Center, Abeokuta,
Ogun state, Nigeria

2.Consultant Pediatric Surgeon,
Department of Surgery,
Federal Medical Center, Abeokuta,
Ogun state, Nigeria

NASJM

Published MEDICAL AND DENTAL CONSULTANTS' ASSOCIATION OF NIGERIA (MDCAN)
DALHATU ARAF SPECIALIST HOSPITAL, LAFIA, NASARAWA STATE

Citation: Akinbode SK, Ogundeyi MM, Adebola MB, Olanrewaju M. Cholelithiasis in sickle cell disease - a case report. *Nasarawa Journal of Medicine* 2024; 1(1): 16–18.

Literature review

Cholelithiasis (gall stones) in SCD is connected to increased bilirubin production as a result of chronic hemolysis, yielding radio-opaque substances formed from calcium bilirubinate crystals.[3,6] Cholelithiasis is rare in otherwise healthy children, but common in predisposing conditions such as SCD, obesity, cystic fibrosis and abnormalities of the biliary trees among others.[10,11] The risk for developing cholelithiasis is higher in the HbSS phenotype compared with other forms of haemoglobinopathies.[4,12] In addition, gallstone formation has been found to correlate with the degree of haemolysis and disease severity.[4] The overall prevalence of childhood cholelithiasis is between 0.13 – 0.22%.[10,11] Prevalence of 25.2% and 31.4% were respectively reported from different hospital-based studies among SCD patients in Brazil[4] and Saudi Arabia[3], while a much lower rate (4.8%) was observed by Ajani *et al*[13] in Nigeria. The incidence of cholelithiasis in SCD increases with age; 58.0% of SCD patients will have stones by age 65[3,4,12] and there is no gender predilection.[4,9]

Gallstones may be clinically asymptomatic. Symptomatic cases could arise from inflammatory changes following calculus obstruction of the cystic duct or the common bile duct presenting as calculus acute cholecystitis and choledocholithiasis respectively.[3,6,13] Symptoms are often non-specific and may include right hypochondrial pain, fever, diaphoresis, jaundice, vomiting etc., some of which are largely indistinguishable from acute hepatopathies and abdominal vaso-occlusive crisis.[6-8,13] Other complications of cholelithiasis include acute pancreatitis, acute cholangitis and obstructive jaundice.[4]

Abdominal ultrasound is a highly recognized modality of choice in diagnosing cholelithiasis and its complications, as it offers a non-invasive and reliable technique for accessing the hepatobiliary tree.[4,6,12]

Radionuclide scan in the form of cholescintigraphy is also useful and has been described as the most accurate method of diagnosing acute cholecystitis.[8,9] Other useful diagnostic modalities include magnetic resonance imaging, magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) which combines diagnostic and therapeutic functions.[8,11]

Laparoscopic cholecystectomy is the gold standard in the management of symptomatic cholelithiasis.[11] Although controversial, elective cholecystectomy is also recommended in SCD patients with asymptomatic gallstones to forestall acute complications and emergency interventions.[4,6] The prognosis of patients with cholelithiasis is excellent following conservative care and cholecystectomy.[11]

We report a patient with sickle cell anaemia who presented with acute calculus cholecystitis to further strengthen awareness of the increased risk of cholelithiasis in children with SCD, a step necessary to avoid misdiagnosis of symptomatic cholelithiasis.

Case summary

O.O., a 14-year-old male adolescent of the Yoruba tribe, known patient with sickle cell anaemia brought on account of yellowish eye discolouration and recurrent abdominal pain of ten days, and vomiting of two days duration. The patient had noticeable yellowish eye discolouration about ten days before admission, no passage of dark urine, and no worsened pallor. The pain was colicky, felt at the right hypochondrial region and radiates to the right lumbar and umbilical regions. It is worsened after food intake, particularly fatty meals. The pain was severe enough to disturb his sleep. He had four different similar episodes in the past two months, each episode lasted for an average of three to five days before spontaneous resolution. Vomiting was non-bilious, and non-bloody, average of one episode per day.

At presentation, he was conscious, in painful distress; he was not febrile (37.2^{0}C), pale and deeply icteric. Body Mass Index was 13.6kg/m^2 (severe thinness). There was right hypochondrial tenderness with positive Murphy's sign and no tenderness in other abdominal regions. There was no hepatosplenomegaly. Abdominopelvic ultrasound revealed features of cholelithiasis, cholecystitis and mesenteric adenitis. Complete blood count showed leukocytosis (14,700/uL) with neutrophilia (82.3%), suggestive of sepsis; the haematocrit was 27%. He had a mildly elevated conjugated (0.7mg/dl) and total bilirubin (1.5mg/dl) on liver function test, other parameters were normal. Initially, he was managed conservatively for calculus acute cholecystitis with intravenous levofloxacin; he had adequate analgesia with acetaminophen, ibuprofen, and oral morphine, together with optimal hydration. He had an open cholecystectomy under general anaesthesia on the 4th day of admission, occasioned by non-resolution of symptoms. Intraoperative finding was a tensed and markedly dilated, thick-walled gall bladder which contained multiple gall stones while the liver architecture was normal, Figure 1. He was discharged on the fourth day after surgery. The patient is presently well on follow-up at the Pediatric haematology clinic.

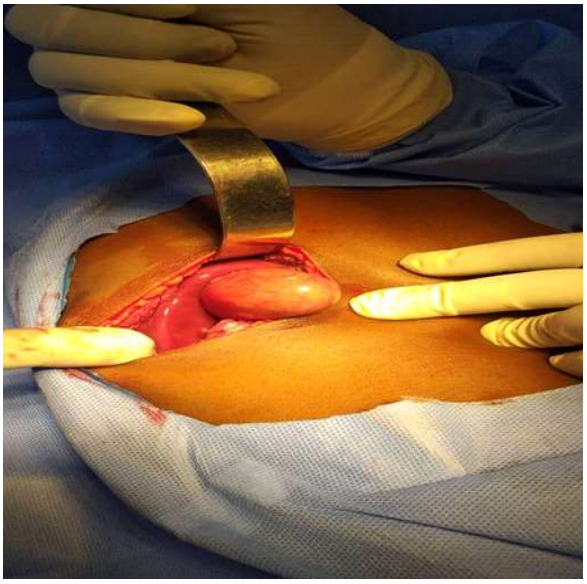

Figure 1: Intraoperative finding of a thick-walled markedly dilated gall bladder.

Discussion

In patients with sickle cell disease, attributable causes of abdominal pain are diverse; ranging from known etiologies such as sickle cell hepatopathies to symptomatic cholelithiasis.[1] Cholelithiasis is a common finding among SCD patients and the majority are symptomatic, as noted by Poddar[9] and Almudaibigh *et al*[4], who observed the proportion of symptomatic gall stones in their studies as 80.0% and 59.4% respectively. As witnessed in the index

patient, symptomatic cholelithiasis invariably presents with abdominal pain, jaundice, and nausea among other clinical features, some of which could suggest other abdominal pathologies in SCD patients.[1,6] For instance, abdominal pain in acute sickle cell hepatopathy and symptomatic cholelithiasis are both felt in the right hypochondrial region, however, the former is associated with hepatomegaly which is often absent in symptomatic cholelithiasis.[7,8] Unlike in sickle cell hepatopathies, cholelithiasis-related abdominal pain is colicky and aggravated by ingestion of fatty food. In addition, palpation of the right hypochondrium leads to the arrest of inspiration in patients with acute cholecystitis (Murphy's sign), a phenomenon conspicuously absent in acute sickle cell hepatopathy.[7,8] Acute splenic sequestration and bowel ischemia are other possible causes of abdominal pain in patients with SCD. While splenic sequestration is associated with massive splenomegaly and left hypochondriac pain, ischemic colitis is accompanied by features of generalized peritonitis.[1,14]

Markers of hepatocellular injury such as mildly elevated liver transaminases may be present in symptomatic cholelithiasis.[7,8] This is in contrast with acute sickle cell hepatopathy where severely deranged hepatocellular enzymes and impaired secretory functions are frequently observed.[6,8] Effects of infection by hepatotropic viruses and hepatotoxic medications are also important causes of hepatocellular injury, hence screening for possible aetiological agents must be done to make an accurate diagnosis.[4,6,12]

The management of the different possible abdominal pathologies differs. Cholecystectomy is offered in symptomatic cholelithiasis while the management of acute sickle cell hepatopathy is mainly supportive vis-à-vis fluid administration, exchange blood transfusion and oxygen therapy.[8,9] Antidotes and antiviral medications are also administered in cases of hepatotoxic ingestions and viral infections respectively. It is therefore imperative to avoid misdiagnosis of the different conditions to allow optimal care. Proponents of prophylactic cholecystectomy opine that such a procedure will improve the care of SCD patients as it enables ruling out symptomatic cholelithiasis as a differential of abdominal pain.[3,9] This intervention is still controversial and risks versus benefits must be thoroughly weighed for such patients. It is therefore beneficial to educate patients with SCD and their caregivers on their propensity to developing gall stones, likely mode of presentation and likelihood of surgery in established cases.[8] This general awareness is necessary to facilitate early diagnosis, improve quality of care and ultimately reduce cholelithiasis-related morbidity and mortality.

Concusion

Symptomatic cholelithiasis could present as acute abdomen in patients with sickle cell disease. A high index of suspicion is necessary to differentiate its clinical presentation from other abdominal pathologies. Screening for cholelithiasis in SCD patients is thus important for early diagnosis, prompt management and adequate follow-up.

Conflicts of interest: None

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Contribution details

Akinbode S.K: concept design, manuscript preparation, literature search and definition of intellectual content
Ogundeyi M.M: concept design, manuscript review, editing and final approval of the published version.
Adebola M.B: manuscript review, editing and final approval of the published version.
Olanrewaju M: manuscript review and editing.