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ORIGINAL ARTICLE

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The significance of biliary sludge in children with sickle cell disease

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Abstract The prevalence of cholelithiasis was studied prospectively by abdominal ultrasound (US) examination in 305 children with sickle cell disease aged 1–18 years (mean 10.45). Gallstones were present in 60 children (19.7%); an additional 50 had biliary sludge only (16.4%). On follow-up of 35 of the 50 children with sludge, 23 (65.7%) had developed gallstones and 5 had already had a cholecystectomy. Five continued to have sludge on follow-up while 7 were reported to have no sludge. Children with US evidence of sludge should be followed up regularly by US, and those who develop gallstones should undergo elective cholecystectomy. For those with biliary sludge only, we recommend elective cholecystectomy if there are hepatobiliary symptoms.

Key words Sickle cell disease · Cholelithiasis · Biliary sludge · Children

Introduction

Cholelithiasis is a common complication of sickle cell disease (SCD), and its incidence increases with age. Its frequency in patients with SCD is variable, ranging from 4% to 55% [1–6]. Another common sequel of SCD is biliary sludge [6], which occurs frequently in compromised patients with extensive burns, in the post-operative period, or in patients requiring total parenteral nutrition, but is not an uncommon finding in other individuals without underlying illnesses. The natural history of gallbladder sludge in patients with SCD is largely unknown. This is a follow-up analysis of 35 children with SCD and biliary sludge outlining their clinical and ultrasonographic (US) courses.

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Materials and methods

In a previous study [6] carried out to determine the frequency and possible risk factors for cholelithiasis in Saudi children with SCD using real-time gray-scale US (GE RT 3000) in 305 children between the ages of 1 and 18 years, we found a 19.7% frequency of gallstones. Biliary sludge was seen in 50 (16.4%) patients. Because the natural history and clinical significance of gallbladder sludge is largely unknown, we retrospectively reviewed the medical records of the 50 children who had sludge on their initial US after they had been followed up for 1 1/2–4 years. Their clinical and radiological courses were reviewed.

Biliary sludge was defined as non-shadowing, echogenic intraluminal sediment [3] (Fig. 1). Gallstones were defined by the presence of shadowing opacities that moved with gravity within a well-defined gallbladder lumen or non-visualization of the gallbladder lumen, often with high-level echoes and shadowing in the area of the gallbladder fossa [3] (Fig. 2). All US tests were performed without sedation on the morning after an overnight fast. Disappearance of biliary sludge was defined as absence of sludge on subsequent repeat US after an initial positive study.

On review, only 35 patients were followed up; the remaining 15 did not undergo further US, and were excluded from the study. The blood hemoglobin (Hb), hematocrit, reticulocyte count, hemoglobin S and F levels, and serum bilirubin were determined for each patient.

Results

Abdominal US was performed in 305 children with SCD (285 SS and 20 sickle-beta-thalassemia [S-β-thal]); 195 (63.9%) had a normal study. Sixty children (19.7%) had gallstones and the remaining 50 (16.4%) had only biliary sludge on their initial US. Patients with gallbladder sludge and gallstones on their initial study were considered positive for gallstones and treated accordingly. Only those with biliary sludge alone are considered in this analysis.

Of the 50 children with biliary sludge, only 35 were followed up. There were 29 homozygous sickle cell (SS) patients and 6 with S-β-thal. Their Hb electrophoresis

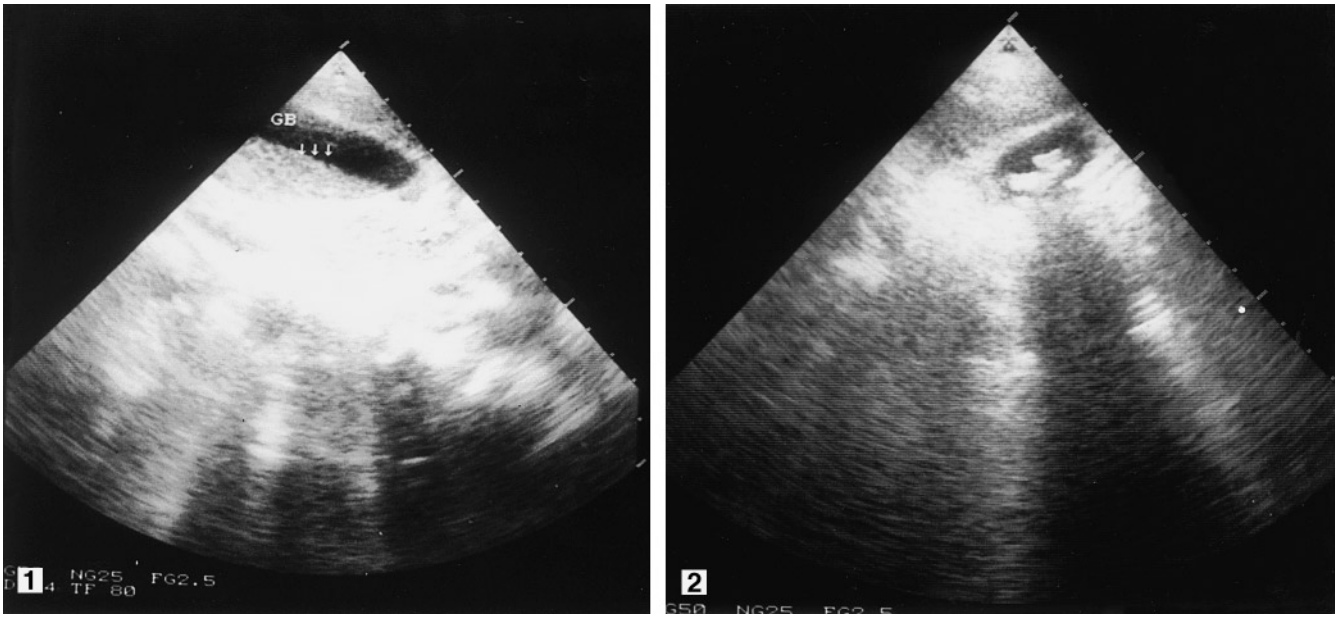

Fig. 1 Gallbladder sludge (*arrows*)

Fig. 2 Multiple gallstones within gallbladder

revealed a mean HbS level of 81.1% (range 63.5–94.5) and a mean HbF level of 16.4% (range 2.7–33). Their ages ranged from 3 to 18 years (mean 12.3). There were 18 males and 17 females. The mean duration from the initial detection of biliary sludge to the follow-up examination was 2.1 years (range 1.5–4). Of the 35 children, 23 (65.7%) had developed gallstones; 5 had already had a cholecystectomy. The remaining 18 were scheduled for elective cholecystectomy. Five patients continued to have biliary sludge on follow-up US; 2 of these gave a history of recurrent attacks of upper abdominal pain suggestive of biliary colic and were advised to have laparoscopic cholecystectomy, but the parents elected to wait. The remaining 7 patients were reported to have no sludge on repeat US. The hematologic variables of these three groups of patients are shown in Table 1.

Discussion

Sickle cell disease, which results from homozygous inheritance of the HbS variant, is one of the commonly inherited hemoglobinopathies worldwide. In the Eastern Province of Saudi Arabia, SCD is common and is characterized by higher levels of both total and fetal Hb [7–9]. The high levels of HbF and the frequently associated alpha-thalassemia contribute to the benign course of SCD in Saudi patients [7, 8]. SCD is characterized by periods of remission and exacerbations called crises. One of the main manifestations of SCD is chronic hemolytic anemia. The chronic hemolysis predisposes affected individuals to form pigmented gallstones. The prevalence of cholelithiasis in SCD patients is variable, ranging from 4% to 55% [1–6]. This variation depends on the age of the patients and diagnostic criteria adopted, as the incidence in patients with SCD increases with age [1–6].

Another common sequel of chronic hemolysis in SCD patients is biliary sludge, a mixture of calcium bilirubinate and cholesterol crystals within viscous bile that contains a high concentration of mucus and proteins [10]. On US it characteristically produces a low-amplitude echo pattern, intraluminal layers in the dependent part of the gallbladder, and no post-acoustic shadowing [3]. The natural history and clinical significance of biliary sludge are not fully known. In previous studies of the incidence of cholelithiasis in SCD patients, no mention was made of its frequency [4, 11]. Sarnaik et al. [3] reported a 6.2% incidence of biliary sludge among

Table 1 Biliary sludge in children with sickle cell disease: analysis of hematologic variables (*Hb* hemoglobin)

Parameter range (mean)	Patients who developed gallstones ($n = 23$)	Patients who continued to have biliary sludge ($n = 5$)	Patients who reverted to normal ($n = 7$)
Hb (g/dl)	5.7–11.2 (8.5)	5.4–9.9 (7.8)	5–10.3 (8)
Hematocrit	18.1–34.8 (26.4)	20.1–28.7 (24.6)	16.5–31.8 (25.6)
Reticulocytes	2.4–15.8 (7.5)	2–14 (5.9)	2–34.4 (10.6)
HbS	63.5–90 (80.5)	76–94.5 (84.6)	83.5–93 (86.7)
HbF	3.5–33 (16.03)	2.7–20.6 (12.3)	7–15.8 (11.95)
Total bilirubin	1.2–13.5 (3.64)	1.3–2.9 (2.03)	1.4–10.8 (3.73)

226 patients with SCD. Winter et al. [12] found a 23% incidence in 75 children with SCD, with 10.7% showing biliary sludge without stones. In our series of 305 children with SCD, the incidence of sludge alone was 16.4% [6]. This variation may be due to the fact that sludge formation and disappearance may be a dynamic process.

The time interval to development of gallstones in patients with biliary sludge is variable; 23 of our patients developed gallstones on follow-up (65.7%), while 5 continued to have biliary sludge. Sarnaik et al. [3] reported 4 convertors to gallstones (28.6%) on follow-up while 6 of their 14 patients with biliary sludge continued to have sludge only. In contrast, Winter et al. [12] found that all of their patients with biliary sludge developed gallstones on follow-up. When compared with patients without SCD, Lee et al. [13] found that only 14.6% of patients with sludge eventually developed gallstones.

Seven of our patients (20%) with sludge alone were reported to have normal follow-up US. Sarnaik et al. [3] reported that 4 of their 14 patients (28.6%) with biliary sludge lost US evidence of the sludge during a 2-year period, while none of Winter et al.'s patients with sludge were reported to convert to normal US [12]. In contrast, the majority of non-SCD patients (78%) [13] showed either disappearance of US features of sludge or had a fluctuating course of disappearance and reappearance. The explanation for this controversy is not known. Biliary sludge can disappear by either spontaneous dissolution or passage into the small intestine. Winter et al. suggested that intraluminal gallbladder sludge may lead to physiologic changes or inflammation that augments gallstone formation [12]. The only difference between SCD and non-SCD patients is that those with SCD have a chronic type of hemolytic anemia that constantly alters the composition of their bile, making it more lithogenic, which is why they have a higher incidence of cholelithiasis and biliary sludge.

None of the factors we studied were predictive of the course of biliary sludge in patients with SCD, and since a high percentage of those patients eventually developed gallstones, patients with evidence of sludge should be followed up regularly by US and those who develop gallstones should undergo elective cholecystectomy. Cholelithiasis may be associated with several complications including acute cholecystitis, pancreatitis, and obstructive jaundice with ascending cholangitis. Specific causes of abdominal pain with a sickle-cell crisis include a hepatic crisis, painful abdominal crisis, splenic sequestration crisis, cholelithiasis, and pancreatitis. Cholecystectomy should simplify the future management of abdominal crises in these patients, as the possibility of acute cholecystitis is eliminated and obviates the problems inherent in operating on these patients on an emergency basis [14]. This is especially so in the era of laparoscopic surgery, which has been utilized successfully in children with SCD [15, 16]. For those with biliary sludge only, we recommend elective cholecystectomy if there are hepatobiliary symptoms.

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