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High Rates of Recurrent Biliary Tract Obstruction in Children with Sickle Cell Disease

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Abstract

BACKGROUND—Individuals with sickle cell disease (SCD) have an increased risk of cholelithiasis from bilirubin stones. Symptomatic biliary tract disease (BTD) includes acute and chronic cholecystitis, obstruction of the common bile duct (CBD), cholangitis, and gallstone pancreatitis. Cholecystectomy is the main treatment strategy for symptomatic patients; however, the prevalence of recurrent BTD following cholecystectomy has not been systematically evaluated. We conducted a retrospective cohort study to describe the recurrence of BTD after cholecystectomy and characterize risk factors for recurrent disease.

PROCEDURE—We identified patients <22 years of age who presented to the Johns Hopkins Children Center with symptomatic BTD from July 1993 to June 2008.

RESULTS—We identified 56 patients with a total of 76 episodes of symptomatic BTD (median age at first event 15.9, range 4.6 to 21.5 years). Eleven of the 56 patients (19.6%) had at least one episode of recurrent symptomatic BTD (median follow-up of 5.3 years). Baseline characteristics were similar between the patients with a single episode of BTD and those with recurrent BTD.

CONCLUSIONS—These results demonstrate that recurrent BTD is a frequent complication of SCD (20% by age 4 years) and often presents as CBD obstruction by stone, despite cholecystectomy. In our cohort, recurrence was not associated with age at first episode, baseline total bilirubin, gender, or genotype of SCD.

Keywords

sickle cell disease; cholecystitis; cholangitis

INTRODUCTION

Individuals with hemolytic anemia, including sickle cell disease (SCD), have an increased risk of cholelithiasis with pigmented stones that result from precipitation of bilirubin and calcium.(1, 2) Elevated serum bilirubin is produced from the breakdown of heme released from hemolyzed erythrocytes.(3) By age 23, the prevalence of cholelithiasis is greater than 50% in those with sickle cell anemia and approximately 20% in hemoglobin SC disease.(4) Cholelithiasis can lead to cholecystitis, choledocholithiasis, cholangitis, and gallstone

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pancreatitis, which are responsible for high levels of morbidity in SCD. Treatment strategies for cholelithiasis often include cholecystectomy for symptomatic patients or abdominal ultrasound screening followed by elective cholecystectomy for asymptomatic patients, in order to prevent the risk of acute complications of biliary tract obstruction, infection and emergent surgery;(5–7) however, the prevalence of recurrent biliary tract disease (BTD) following cholecystectomy has not been systematically evaluated.

We hypothesized that the prevalence of recurrent BTD was higher in children and young adults with SCD compared to the general population (10%) and that known risk factors for cholelithiasis in SCD (total bilirubin, age) and in general population (age, female sex, pregnancy, and use of cephalosporins) would be associated with recurrent disease.(3, 8) We present observations from a cohort of children and young adults with SCD and symptomatic BTD.

METHODS

We conducted a retrospective cohort study to describe the recurrence of BTD after cholecystectomy and characterize risk factors for recurrent disease. We included patients (age <22 years) who presented to Johns Hopkins' Children Center with symptomatic BTD from July 1993 to June 2008. We identified cases from the hospital's discharge database using International Classification of Diseases, Revision 9 (ICD-9) codes for SCD 282.41, 282.41, 282.6, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69) and BTD (574.00, 574.01, 574.10, 574.11, 574.30, 574.31, 574.40, 574.41, 574.50, 574.51, 574.60, 574.61, 574.70, 574.71, 574.80, 574.81 574.90, 574.91, 576.1, 577.0) and Current Procedural Terminology (CPT) codes for surgeries and procedures of the biliary tract (51.10, 51.11, 51.22, 51.23 51.41, 51.43, 51.81, 51.82, 51.84, 51.87, 51.88) and by reviewing dictated discharge summaries. As this was a retrospective study, all treatment decisions including the criteria for cholecystectomy, transfusion, and discharge were at the discretion of the attending physician.

DEFINITIONS

Radiological detection of biliary stone(s) in symptomatic patients was used as the diagnostic criteria for BTD (biliary sludge alone was not included). We recorded episodes of acute and chronic cholecystitis, cholangitis, bile duct obstruction, clinical or laboratory pancreatitis, and surgical procedures during the entire follow-up period.

Acute cholecystitis was defined as an episode of right upper quadrant or epigastric pain with fever or positive Murphy's sign or imaging consistent with acute cholecystitis (ultrasound demonstrating gallstones and gallbladder wall thickening, pericholecystic fluid, sonographic Murphy's sign or cholescintigraphy demonstrating cystic duct obstruction).(9)

Chronic cholecystitis was defined per the surgical pathology report.(10)

Common bile duct (CBD) obstruction was defined as total bilirubin 150% of baseline or 7.5 mg/dL or direct bilirubin 1.5 mg/dL and upper abdominal pain with evidence of cholelithiasis, or imaging demonstrating CBD dilatation or obstruction by stone.(11)

Cholangitis was defined as evidence of infection (fever or positive blood or bile culture) and CBD obstruction.(9)

Clinical pancreatitis was defined as amylase greater than three times the upper limit of normal and epigastric pain or imaging study showing findings consistent with pancreatitis. (12)

Laboratory pancreatitis was defined as amylase greater than three times the upper limit of normal without the clinical criteria for pancreatitis.(13)

MEDICAL RECORD EXTRACTION

A single reviewer collected data from the paper and electronic records using a structured form, with confirmation by a second reviewer for 20% of the episodes and all recurrences. These data included presenting symptoms, baseline characteristics, comorbid conditions, medications, type and frequency of complications, laboratory and radiographic evaluation, treatments given, duration of hospitalization and recurrence post cholecystectomy. We adjusted costs to 2006 dollars, using a 5% annual rate of inflation.

STATISTICAL ANALYSIS

We used the Wilcoxon rank-sum and Fisher exact tests to compare continuous and dichotomous variables and Kaplan-Meier estimates and the log-rank test for the equality of survivor functions between groups. We performed all statistical analyses with Stata 11.0 (College Station, TX).

RESULTS

We identified 56 patients with a total of 76 episodes of symptomatic BTB (median age at first event 15.9, IQR 12.8, 18, range 4.6 to 21.5 years). More episodes were in patients with sickle cell anemia (90%) than hemoglobin SC disease (9%), or sickle- β^0 thalassemia (1%). Most patients underwent cholecystectomy shortly after diagnosis (82% within 3 months), but those who did not were at high risk of recurrent BTB (50% by 6 months after the initial event). The risk of recurrence after cholecystectomy was much lower (8% by 4 years, $P<0.0001$ (Figure 1).

Eleven of the 56 patients (19.6%) had at least one episode of recurrent symptomatic BTB (median follow-up of 5.3 years, IQR 3.2, 8.3), with a 20% risk of recurrence after 4 years using Kaplan-Meier estimates (Figure 1). Eight patients had one recurrence, one patient had two, one had four, and one had six, for a total of 20 recurrent episodes. Seven episodes occurred before and 13 after cholecystectomy, for a rate of recurrence of 30 (95% CI 12 -62) per 100 person years before and 3.9 (95% CI 2.1 -6.6) after cholecystectomy. Baseline characteristics, including age, sex, hemoglobin genotype, total hemoglobin, total bilirubin, use of hydroxyurea, and prior admissions for pain or fever (a proxy for treatment with ceftriaxone) were similar between the patients with a single episode of BTB and those with recurrent BTB (Table). Costs were significantly lower for the initial hospitalization for patients that recurred (\$8,234, IQR 5,204, 11,395) because they were less likely to have a cholecystectomy during that hospitalization than for patients that did not develop recurrent BTB (\$13,509, IQR 10,179, 23,466, $P=0.02$). Costs for recurrent episodes (\$12,455, IQR 9,685, 19,416) were similar to those of the initial hospitalization (\$12,668, IQR 8,561, 22,582).

Seven patients had pancreatitis (four clinically and three laboratory defined, including 6 with their initial presentations). Four of the seven episodes of pancreatitis were secondary to obstruction by stone or sludge and two from strictures in the CBD. There was radiographic evidence of pancreatitis in 2 of the 4 clinical cases (enlarged pancreas by ultrasound in one, hypodense and edematous with peripancreatic fluid by MRI in the other). There were 45 episodes of CBD obstruction in 32 patients (four with cholangitis) including 28 patients (50%) with CBD obstruction during their initial episode.

Treatment for symptomatic BTB was laparoscopic cholecystectomy in 51 (92%), open in 4 patients (7%), with 5 intraoperative cholangiograms and 26 endoscopic retrograde

cholangiopancreatographies. Cholecystectomy was not performed in one patient. Two patients had significant complications after laparoscopic cholecystectomies (one acute chest syndrome and the other bile peritonitis secondary to a bile leak requiring intensive care for 20 days); however, median length of hospitalization and costs were not statistically significantly different for laparoscopic [6 days (IQR 3,9), \$13,115 (IQR 9243, 22,513)] compared to open cholecystectomy [9 days (IQR 4,20, p-value 0.28), \$29,510 (IQR 11,723, 46,422, p-value 0.16)]. Twenty-four recurrent episodes were usually treated by ERCP (15 episodes) or observation (9 episodes), with median length of stay of 5 days (IQR 4, 8) and costs of \$12,445 (IQR 9,464, 21,364). The four significant complications related to ERCP included respiratory depression during the procedure (1), laboratory pancreatitis (1), worsening abdominal pain, acute chest syndrome (1), and fever of 39.1° C (1) after the procedure. Most recurrent episodes (17) met the definition for CBD obstruction and small stones were identified by ultrasound or during ERCP. Only one recurrent episode was associated with clinical pancreatitis.

DISCUSSION

CBD obstruction may be a more common complication in children and young adults with SCD and BTd (50% in this study) than in the general population (10–15%) or than previously appreciated in SCD (18 to 30%). (4, 14) It is often missed by abdominal ultrasound and may only be apparent by intraoperative cholangiography or ERCP.(15) To our knowledge, there are only three published cases of CBD obstruction following cholecystectomy in patients with SCD; however, we found that by 4 years after cholecystectomy, 8% of patients had recurrent BTd, with CBD obstruction by stone in 68% of these patients (5.5% of those followed). This is similar to the 9.8% rate for recurrent stone seen after cholecystectomy and endoscopic sphincterotomy for primary or secondary choledocholithiasis in adults without SCD, but no comparable data are available in children. (8) The recurrences in children and young adults with SCD were mostly caused by small stones and were not associated with known risk factors for cholelithiasis in SCD. We used total bilirubin as a proxy for risk secondary to polymorphisms in bilirubin UDP-glucuronosyltransferase 1A1 (UGT1A1) gene, as promoter polymorphisms in this gene have been implicated in the development of hepatobiliary disease in children with SCD, but no association was seen with bilirubin and recurrent BTd in our series.(16) It seems likely that other unidentified factors, genetic, environmental and anatomic factors, may be associated with recurrent BTd in SCD.

Our study found no difference in cost between laparoscopic and open cholecystectomy, perhaps due to the small numbers of open cholecystectomies. Costs for the initial hospitalization were lower in the group that recurred, but at the expense of additional admissions for recurrent BTd. This provides some support for cholecystectomy during the initial admission. We used number of days of fever, a surrogate measure, to approximate cephalosporin use, and found no relationship with recurrent BTd in our cohort.

Strengths of this study include the multiple methods used to identify cases, including a discharge database (with ICD-9 and CPT codes) and discharge summaries. We also used rigorous definitions of complications and a structured data extraction form. Limitations include the small sample size and retrospective collection of data from a single medical institution. This study is also possibly limited by missing cases, selection of more severe cases and some missing data for baseline values. In addition, we may have potentially misclassified some cases of sickle hepatopathy with concomitant asymptomatic cholelithiasis as BTd. We believe this was a rare occurrence as the pathologic examination of the gallbladder usually supported the diagnosis of cholecystitis and most patients with CBD obstruction had an obstructing stone and/or dilation of the CBD by imaging.

The prevalence of recurrence observed in this study indicates that providers should have a high index of suspicion for CBD obstruction and gallstone pancreatitis in children with SCD and a prior history of BTB presenting with abdominal pain. Further studies, including multicenter prospective studies, are needed to elucidate the risk factors for recurrent episodes of symptomatic BTB and to evaluate potential treatments to prevent recurrence. These could include surgery with the first episode or strategies to decrease hemolysis and therefore hyperbilirubinemia (hydroxyurea or a chronic transfusion protocol).(17)

Acknowledgments

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Abbreviations

SCD	indicates sickle cell disease
BTB	biliary tract disease
CBD	common bile duct
ERCP	endoscopic retrograde cholangiopancreatography

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Figure 1.

Time to recurrence of biliary tract disease before and after cholecystectomy in children and young adults with sickle cell disease. Follow-up was truncated at time of cholecystectomy.

Table IBaseline Characteristics of Patients by Recurrence of Cholelithiasis [Median (IQR) or Mean $\pm$ SD]

Variable	No Recurrence N=45	Recurrence N=11
Age (years)	15.2 $\pm$ 4	13.9 $\pm$ 5
Male sex (%)	53%	55%
HbSS (%)	89%	91%
Hemoglobin (g/dl)	8.1 $\pm$ 1.5	8.1 $\pm$ 1.4
Total bilirubin	3.9 $\pm$ 2.6	5.2 $\pm$ 2.6
Hydroxyurea use (%)	14%	7%
Pain admissions (days)	9 (0, 25)	13 (0, 24)
Fever admissions (days)	2.5 (0, 8)	2 (0, 7)
Body Mass Index (kg/m ²)	18.6 (15, 21)	17.0 (15, 19)

IQR indicates interquartile range; SD, standard deviation; HbSS, sickle cell anemia; *p> 0.05 for all of the variables between the two groups, except p<0.05 for hospital costs