Cholelithiasis and Cholecystitis in Children

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With advances in medical technology, including intensive care, new medications, alterations in the composition of parenteral nutrition, and the institution of minimally invasive surgery, our understanding of the spectrum of diseases of the gallbladder resulting in stone formation or inflammation, and the management of these disorders has changed over the past few decades. The discussion herein focuses on our thinking about the current diagnosis and treatment for these disorders.

ETIOLOGY

CONGENITAL anomalies of the gallbladder are rare, and are often associated with cholelithiasis.[1-4] Agenesis, duplication, a bilobed gallbladder, and ectopic location are the most frequently encountered malformations.[5] Congenital stenosis of the cystic duct has been documented as a cause of gallbladder stasis/obstruction, resulting in gallstone formation. Uno et al[6] noted that patients with biliary dilatation with stricture of the intrahepatic bile ducts are likely to develop intrahepatic cholelithiasis after surgical excision of a choledochal cyst, and suggested that the stenoses be relieved by whatever means feasible at the initial surgery.

Cholecystitis and cholelithiasis are increasing in frequency in infancy, childhood, and adolescence[1-4]; the incidence is reported to be between 0.15% and 0.22%. Gallstones are generally classified according to type. Any disturbance in the concentration of lecithin, bile salts, or cholesterol renders the bile lithogenic and predisposes the child to form cholesterol stones that probably result from poor solubilization of cholesterol, stasis, and nucleating factors. Pigmented stones can be black or earthy brown. Black pigmented stones are usually associated with a hemolytic process or occur after ileal resection, or in patients receiving total parenteral nutrition (TPN) and are more common among Orientals. Hemolysis is seen in sickle-cell disease, hereditary spherocytosis, thalassemia major, pyruvate kinase deficiency, hexose-kinase deficiency, autoimmune hemolytic anemia and after open-heart surgery and insertion of cardiac valves. Earthy calcium bilirubinate stones can develop in patients with infected bile or biliary strictures. The bile of these patients contains an excess amount of unconjugated bilirubin and glucuronic acid. Unconjugated bilirubin then forms calcium bilirubinate when stasis exists and nucleating factors are present. Gallstones in children with short-bowel syndrome or inflammatory bowel disease maintained on TPN are predominantly pigmented stones.

Gallstones have been recognized in utero by prenatal ultrasound with spontaneous resolution occurring by 1 month of age.[7] Cholelithiasis in neonates and infants is associated with infection, TPN,[8] long-term furosemide therapy,[9] polycythemia, phototherapy, and following exchange transfusion. Up to 43% of children receiving long-term TPN develop gallstones.[9a] In approximately 44% of these patients sludge is observed before stone formation.[9a] The administration of large amounts of amino acids and a high ratio of non-protein (kcal/mL) enhances the risk for formation of gallstones and sludge. Conversely, they can be prevented by the administration of appropriate amounts of fat.

Other possible etiologic factors in newborns include dehydration, short-bowel syndrome due to extensive small bowel loss,[10,11] ileal resection for necrotizing enterocolitis, midgut volvulus, cystic fibrosis, multiple intestinal atresias, and after longitudinal intestinal lengthening.[12] In addition, chronic maternal use of morphine may predispose infants to bile sludge followed by gallstone formation.

Total parenteral nutrition-induced liver disease develops in 40% to 60% of infants who require long-term TPN for intestinal failure.[12a] The clinical spectrum includes cholestasis, cholelithiasis, hepatic fibrosis with progression to biliary cirrhosis, and the development of portal hypertension and liver failure in a significant number of infants who receive TPN. The pathogenesis is multifactorial and is related to prematurity, low birth weight, and the duration of TPN. The degree and severity of the liver disease is related to recurrent sepsis including catheter related sepsis, bacterial translocation, and cholangitis. Lack of enteral feeding leading to reduced gut hormone secretion, reduction of bile flow, and biliary stasis may be important mechanisms in the development of cholestasis, biliary sludge, and cholelithiasis.

Recently, manganese toxicity has been recognized in children with hepatic dysfunction on TPN.[12a] Although there is a definite relationship between the degree of manganese toxicity and hepatic decompensation, it is not clear whether this is a primary mechanism or whether the high levels are related to reduced biliary excretion of

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manganese. The administration of ursodeoxycholic acid may improve bile flow and reduce gall bladder and intestinal stasis. As survival from isolated intestinal transplantation improves, this therapeutic option should be considered before TPN-induced liver disease becomes irreversible and combined liver and small bowel transplantation is required.[13]

In sickle cell disease, cholelithiasis has been reported in 42% of subjects with the beta 5 beta 5 form, and in 27% of subjects with the beta 5 beta th form.[14] There is a greater incidence of cholelithiasis during the first years of life with the beta 5 beta 5 form of the disease than with the beta 5 beta th form. In another study, Al-Salem and Qaisruddin[15] investigated the prevalence of cholelithiasis using abdominal ultrasound in children with sickle cell disease. Gallstones were present in 20% of children, an additional 16% had biliary sludge only. On follow-up, two-thirds of the 50 children with sludge had developed gallstones and five had already had a cholecystectomy. Five continued to have sludge on follow-up while seven were reported to have no sludge. They recommended that children with evidence of sludge should be followed up regularly by ultrasound and those who develop gallstones should undergo elective cholecystectomy. We prefer to perform elective cholecystectomy only if there are hepatobiliary symptoms.

The incidence of cholelithiasis in children with thalassemia major varies from 2% to 23% and increases with age. Gallstones are observed in about 6% of children 6 to 10 years of age and 45% of children 11 to 14 years of age. The risk of cholelithiasis may be decreasing in these children as a result of hypertransfusion therapy which blocks the bone marrow so that the fragile cells of thalassemia major are no longer produced.

The incidence of cholelithiasis in hereditary spherocytosis is 43% to 63% and is slightly more common in girls than boys. Abdominal ultrasound examination should be performed before planned splenectomy to detect the presence of gallstones.

Gallstones can develop in older children and adolescents as well. Children with ileal resection or dysfunction do not appear to be at risk for cholesterol cholelithiasis before puberty. However, the development of biliary cholesterol supersaturation after puberty may predispose them to gallstone formation in adulthood.[16]

In the absence of an underlying hematologic disorder, most gallstones are associated with obesity, adolescent pregnancy, a positive family history for cholelithiasis, the use of oral contraceptives, or as a complication of choledochal cyst. An increased risk of cholelithiasis also has been documented in children receiving treatment for Wilm's tumor, neuroblastoma, Hodgkin's disease, and non-Hodgkin's lymphoma. Still, the origin of gallstones in approximately 80% of pediatric patients remains unknown.[17] While there is no sex predilection, females begin to predominate in adolescence with a ratio of 11:1 to 22:1, probably due to the influence of estrogen.

Gallbladder dyskinesia, characterized by poor gallbladder contractility and the presence of cholesterol crystals in the bile, is most likely an early stage of cholesterol gallstone formation. They increase in frequency with age. Symptoms suggestive of biliary colic in children without evidence for cholelithiasis may frequently represent biliary dyskinesia.[18]

Cholelithiasis can be due to Salmonella infection of the gallbladder,[19,20] and Ceftriaxone therapy has been known to induce reversible precipitates or biliary pseudolithiasis which can be reversed by discontinuation of the drug.[21-23]

Other patients at risk may be liver transplant recipients whose donors were prone to develop lithogenic bile. Cao et al suggest analyzing the bile at the time of procurement, and, depending on the cholesterol and bile acid composition, recommend FK[506] be used in these patients with or without the addition of ursodeoxycholic.[24]

The incidence of gallstones in children who are heart transplant recipients is approximately 16% at a mean of 4 months post-transplant.[25] Patients who have been on extracorporeal membrane oxygenation are also at risk for gallstones,[26] and should undergo cholecystectomy if stones develop.

CHOLECYSTITIS

Acute noncalculous distention of the gallbladder, hydrops, is characterized by severe edema around the gallbladder and common bile duct. Older infants and children may manifest fever, a right upper quadrant mass, and abdominal tenderness on palpation; whereas a mass may be the only finding in neonates. In newborns, acute hydrops has been observed in septic infants and also has occurred in a patient with cystic duct agenesis. In older infants and children, hydrops may accompany scarlet fever, leptospirosis, and Kawasaki disease (mucocutaneous lymph node syndrome). In the latter instance, the cystic duct and common bile duct are surrounded by enlarged lymph nodes.[27]

Acalculous cholecystitis tends to occur as a complication of severe illness, or as a sequela of surgery, burns or multisystem trauma, massive blood transfusion, and various infections including pneumonia, generalized sepsis, typhoid, salmonella, otitis media with meningitis, giardiasis, and Kawasaki disease. The underlying features involved in the pathogenesis include dehydration, adynamic ileus, gallbladder stasis, treatment with TPN, and hemolysis from multiple transfusions. According to Shapiro et al[28] acute acalculous cholecystitis accounts for 2% to 15% of all cases of acute cholecystitis, and the inci-

dence of acute acalculous cholecystitis may be as high as 32% in children undergoing cholecystectomy.

An unusual cause of cholecystitis is torsion of the gallbladder. This condition can be diagnosed presurgically by noting a dislocation of the gallbladder on the presurgical ultrasound.[29]

Cholecystitis is known to be one manifestation of cytomegalovirus disease in renal transplant patients[30] and may be seen in critically ill children such as those undergoing cardiac surgery.[31]

Cholecystitis also can occur after spinal fusion and instrumentation in children. When diagnosed early, conservative, nonsurgical therapy may be sufficient.[32]

Eosinophilic cholecystitis can be diagnosed by peripheral blood eosinophilia or a positive bone marrow aspirate.[33] These patients respond promptly to prednisone therapy.

DIAGNOSIS

Symptomatology and associated medical history are more important in diagnosing cholelithiasis than are laboratory tests. Jaundice is the most common symptom (90%) in children less than 1 year of age. Overall, the most common presenting symptom is vomiting (60%).[34] While right upper quadrant pain in the absence of vomiting is not significant, as this occurred only once.

Gangrenous acalculous cholecystitis can occur in premature infants and may be confused with necrotizing enterocolitis.[35] The diagnosis of acalculous cholecystitis in the newborn can be diagnosed with a combination of ultrasound and radionuclide scanning.[36]

In smaller children, the symptoms of acalculous cholecystitis include fever, right upper quadrant pain, nausea, vomiting, and occasionally diarrhea when the underlying infection is caused by a pathogenic intestinal organism. Tenderness to palpation and muscle guarding are noted on physical examination. A right upper quadrant mass is sometimes palpable and must be distinguished from acute hydrops. Leukocytosis and jaundice are often observed, and serum amylase may be elevated signifying associated pancreatitis. The diagnosis is confirmed by ultrasound.

Gallbladder contractility may be assessed with ^{99m}Tc diisopropyl iminodiacetic acid in response to cholecystokinin injection. Ejection fractions in patients with biliary dyskinesia are usually less than 35% to 40%.

Children with acute cholecystitis can present with fever, nausea, vomiting, right upper quadrant abdominal tenderness, and guarding. A right upper quadrant mass is occasionally present. While jaundice may indicate choledocholithiasis, more often it is simply due to hemolysis. In patients with chronic cholecystitis and cholelithiasis, the physical examination is often normal. In instances of acute cholecystitis, laboratory tests may demonstrate an elevated white blood cell count and left shift on the differential smear. With choledocholithiasis, elevation of serum direct bilirubin, alkaline phosphatase, and gamma-glutamyl transferase levels can be observed. Serum amylase may be elevated with associated pancreatitis.

Chronic cholecystitis and cholelithiasis are much more common than acute cholecystitis in children. Pain is less well-localized in younger children and is often confused with that of appendicitis. Chronic cholecystitis is commonly characterized by recurrent bouts of right upper quadrant pain associated with meals. The pain is usually much less specific and only rarely associated with fatty food intolerance.

The most accurate and useful diagnostic test is the ultrasound examination.[37-39] Both real-time and gray-scale ultrasound studies allow the recognition of echogenic images and acoustic shadows with the mobility in the gallbladder and assessment of gallbladder size and wall thickness and the diameter of the common bile duct. The ultrasound study has an accuracy of approximately 96%. Cholescintigraphy with technetium-^{99m}-labeled iminodiacetic acid compounds is the most useful test to assess the patency or obstruction of the cystic duct and is the procedure of choice to diagnose acute cholecystitis. In patients with acute cholecystitis, the isotopic scan will demonstrate flow from the extrahepatic biliary system into the intestine without visualization of the gallbladder. False-positive scans may result in fasting patients or those receiving TPN. Administration of intravenous morphine before the scintigram is useful in such cases as it will cause spasm of the sphincter of Oddi, resulting in an increase in common bile duct pressure and enhance visualization of the gallbladder, thus excluding the diagnosis of cholecystitis. This test has a sensitivity near 100% and a specificity of 95%. Cholescintigraphy also is useful in detecting common bile duct obstruction or a choledochal cyst.

Spiral computed tomography cholangiography is a relatively new imaging technique that results in biliary opacification and a three-dimensional reconstruction. This study, as well as the magnetic resonance imaging cholangiogram, proves useful in complicated cases of obstruction or pancreatitis and often obviates the need for endoscopic retrograde cholangiopancreatography (ERCP) or other forms of cholangiography.[40]

TREATMENT

Spontaneous resolution of gallstones in some neonates and infants up to age 3[41] has been observed on serial ultrasound examinations.[42] It may be difficult to differentiate biliary sludge from cholelithiasis in premature infants, and some cases that resolve may have sludge rather than stones. Resolution of stones may occur as

soon as 2 to 20 days after cessation of TPN therapy. We recommend nonsurgical therapy for noncalcified, asymptomatic, TPN-related gallstones (for as long as 9 to 12 months) and cholecystectomy for symptomatic children with TPN-associated gallstones and those with calcified radiopaque gallstones, as these are unlikely to resolve spontaneously. Surgical treatment in neonates or infants with cholelithiasis may be necessary for complications of acute inflammation or cholangitis. Therapeutic options include surgical cholecystectomy or cholecystotomy with stone removal and irrigation. Attempts at percutaneous puncture of the gallbladder or intrahepatic ducts with subsequent irrigation of the biliary tract to clear obstructing biliary sludge and stones is associated with cholangitis in 40% of patients.[27]

Children with gallstones and typical symptoms of right upper quadrant or epigastric pain with food intolerance should undergo cholecystectomy. In one study, 82% of children with cholelithiasis and atypical symptoms had improvement with dietary manipulation. Pediatric patients with gallstones that are asymptomatic or associated with atypical symptoms can be safely followed without complications.[43]

The treatment of hydrops is conservative. Antibiotics are used when appropriate for septic patients, and when possible, early enteral feedings to stimulate gallbladder contraction and emptying. These patients should be followed by serial ultrasound examinations and if distention and pain persist or increase a cholecystostomy may be helpful. If the gallbladder wall appears gangrenous, or if cystic duct obstruction is detected, a cholecystectomy should be performed.

The treatment for mild cases of acalculous cholecystitis includes nasogastric suction, intravenous fluids, and appropriate parenteral antibiotics. The patient's course is followed by serial ultrasound examinations. Persistence of a mass and/or increased distention and clinical deterioration constitute indications for surgical intervention. Cholecystostomy is reasonable for bothersome distention; however, cholecystectomy should only be carried out for inflammation, the presence of purulent exudate, or gangrenous changes in the gallbladder wall. Gallbladder infarction has also been observed as a result of arteritis in patients with Kawasaki disease.

Amphotericin B is effective in the treatment of Candida cholecystitis.[44]

Gamba et al[45] explored the possibility of medical treatment of gallstones with ursodeoxycholic acid or chenodeoxycholic acid in children. All patients had radiolucent stones with a maximum diameter of 10 mm and a normally contractile gallbladder. The stones disappeared completely in two of the 15 children, but later returned. All symptomatic patients became symptom-free. The investigators concluded that ursodeoxycholic acid is ineffective in the permanent elimination of gallstones in children but can serve to temporarily relieve symptoms.

Extracorporeal shockwave lithotripsy used in conjunction with oral therapy has limited use in children and is expensive, painful, and has a high recurrence rate. Percutaneous endoscopic cholecystolithotomy is invasive, has a high risk of gallstone recurrence, and is similarly poorly suited for infants and young children. The exception to this may be a select group of orthotopic liver transplant recipients for whom percutaneous transhepatic electrohydraulic lithotripsy using an 11 French flexible ureteroscope may be the approach of choice.[46]

Choledocholithiasis with cholestatic jaundice in infants usually requires therapeutic intervention, although spontaneous resolution has been reported in 28% of patients.[47] If choledocholithiasis with obstructive jaundice occurs, ERCP and endoscopic sphincterotomy with stone removal can be used to clear the common bile duct[47] even in infants. If gallstones remain after clearing the common bile duct, a formal cholecystectomy should be performed, since recurrent complications are likely. If endoscopic sphincterotomy is unsuccessful or if the child is too small for ERCP, a procedure with irrigation of the common bile duct through the cystic duct or a transduodenal sphincterotomy may be helpful. If bile duct perforation has occurred, early peritoneal irrigation and drainage usually provide effective treatment.

Sickle cell disease patients with gallstones have an average of more than 10 hospitalizations and 25 ambulatory visits annually, mostly for infectious complications.[48] Those without gallstones have an average of only 4 hospitalizations and 13 ambulatory visits per year. For children with sickle cell anemia and gallstones, elective cholecystectomy (or perhaps cholelithotripsy) can reduce the high morbidity caused by infection.[48] As many as 50% of previously asymptomatic patients will require operation within 3 years because of significant complications or symptoms of acute cholecystitis. Careful presurgical preparation of the child with sickle-cell anemia is essential to avoid sickling of the abnormal red blood cells which may be precipitated by hypoxia, hypothermia, acidosis, hypovolemia, and a high level of hemoglobin S. This applies in particular to patients with Hemoglobin SS, SC, and S Beta thalassemia. Patients who are having a major procedure should be admitted the day before surgery.[17] Presurgical transfusion of 10 to 15 mL/kg of sickle dex negative red blood cells is given to increase the hemoglobin to 10 to 11 gm/dL. During fasting, intravenous hydration is given at 1.5 × maintenance. Patients who have a baseline hemoglobin of 9 to 11 gm/dL may not need transfusion. The decision to withhold transfusion should be made in conjunction with a hematologist. If urgent surgical intervention is re-

quired, either an exchange transfusion or red cell phresis should be carried out before the procedure.

Cholecystectomy is recommended for all symptomatic patients with thalassemia or spherocytosis, as well as those undergoing splenectomy in whom a presurgical ultrasound demonstrates gallstones. However, some surgeons prefer simple cholecystotomy with removal of stones at the time of splenectomy for spherocytosis.

Cholecystectomy

Davidoff et al[49] were among the first to describe the technique of laparoscopic cholecystectomy in children. The benefits of laparoscopic cholecystectomy include decreased pain and ileus after surgery, shortened hospitalization, and improved cosmesis. Laparoscopic cholecystectomy is safe and efficacious in children, comparing favorably with traditional cholecystectomy.[50-55] This technique is of particular value in the obese child,[56] for cholecystitis in pregnancy,[57,58] and in managing the biliary complications of heart transplant patients.[25,59]

In a comparison between 29 laparoscopic and 23 open cholecystectomies for symptomatic cholelithiasis, the requirement for postsurgical parenteral analgesia for laparoscopic cholecystectomy was significantly less than for the open procedure.[60] The mean length of hospitalization for laparoscopic cholecystectomy was only one third that of the open procedure. Although the average operating room costs per case for laparoscopic cholecystectomy were significantly more expensive than for the open procedure, laparoscopic cholecystectomy was significantly less expensive overall because the period of hospitalization was significantly shortened.[60]

Holcomb et al[74] reported their experience with 100 consecutive laparoscopic cholecystectomies. Patients ranged in age from 25 months to 230 months, with a mean of 105 months. Only 19 patients had hemolytic disease as the etiology for their cholelithiasis. Two patients had biliary dyskinesia. Seventy-eight patients underwent an elective operation. Twenty-two children required urgent hospitalization because of complications from their cholelithiasis: acute cholecystitis (n = 7); jaundice and pain (n = 6); gallstone pancreatitis (n = 5); acute biliary colic (n = 4). All 6 patients who presented with jaundice underwent ERCP before their laparoscopic cholecystectomy. Two patients required laparoscopic choledochal exploration. The surgical time and postsurgical hospitalization were significantly longer in the complicated group when compared with the elective patients. No significant complications such as the need for additional surgery, injury to the choledochus or to other viscera, bile leak, or retained choledocholithiasis occurred. Most of our cholecystectomies in children have been for symptomatic cholelithiasis secondary to sickle cell disease. In patients who present with recurrent abdominal pain, we usually remove the appendix concurrently. Of interest is the finding of pathology in 50% of the appendices removed from these children. The pathology was mixed, demonstrating scaring in some and inflammation in others.

Klin et al[75] studied bile cultures from 30 children undergoing laparoscopic cholecystectomy and decided, on the basis of only one positive bile culture, that routine cultures are not necessary and that bile spillage during the course of routine cholecystectomy is not an indication for the use of antibiotic.

Lugo-Vicente[76] recently studied infants and children requiring cholecystectomy. The mean age was 15 years. Females (76%) with classic biliary symptoms predominated; 12% of the patients developed gallstone pancreatitis and 7% developed jaundice. Abnormal liver chemistry values, obesity, and elevated triglyceride levels comprised the most significant predisposing factors. Indications for surgery were cholelithiasis 86%, gallbladder dyskinesia in 12%, and sludge/polyp in 2%. Fifty-nine cholecystectomies (71%) were performed laparoscopically and 29% were open. Choledocholithiasis in 7% was managed by open extraction with t-tube placement or endoscopic papillotomy followed by laparoscopic cholecystectomy. No major ductal complication was identified. The predominant pathologic finding was chronic cholecystitis, including the subgroup with biliary dyskinesia. Statistical comparison showed that laparoscopic cholecystectomy is superior to open cholecystectomy in regard to length of stay, diet resumption, use of pain medication, operating time, and cosmetic results.

The role of routine intraoperative cholangiography is somewhat controversial. While some authors believe that it should be routine,[61,62] the majority recommend selective studies.[63-68] Cholangiography can be performed by any one of several methods. Commercial catheters have been produced which can be passed through a cannula. Unfortunately, this results in a loss of exposure, as one of the graspers must be removed. Holcomb and colleagues use the Kumar clamp (Nashville Surgical Instruments, Springfield, TN), which is a reusable device designed to occlude the proximal gallbladder while providing needle access to the distal gallbladder just proximal to the cystic duct, for the easy introduction of contrast material to outline the biliary duct.[62,69]

We have treated 10 cases with common duct stones by incising the cystic duct and dilating it with a balloon catheter[70] to allow insertion of another endoscope into the bile duct.[71,72] For a pediatric choledochoscope, we have found it convenient to use a pediatric cystoscope. This allows for good visualization and provides access for irrigation and instrumentation (eg, the passage of a stone basket). A second camera can be attached to the

choledochoscope so that the surgeon can see intraductal and extraductal anatomy simultaneously. Usually, after the endoscope is removed from the duct, the cystic duct stump can be ligated in the standard fashion.[73]

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