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Biliary Disease in Children

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Abstract Biliary diseases in children are infrequent; however, they can be associated with high morbidity and mortality if an accurate diagnosis is not made and adequate treatment provided in a timely fashion. Biliary atresia, choledochal cysts, gallbladder disease, and Alagille syndrome can be associated with similar clinical symptoms, laboratory findings, and radiographic findings, which makes accurate diagnosis difficult. The correct treatment for each of these clinical entities is different and can significantly reduce morbidity and mortality from these diseases. In this article, we discuss the epidemiology, approach to diagnosis, prognosis, and treatment modalities for these four disease processes.

Keywords Biliary atresia · Choledochal cyst · Cholelithiasis · Biliary dyskinesia · Kasai · Alagille syndrome · Hyperbilirubinemia · Hepatoportoenterostomy · Hepatic iminodiacetic acid scan · Magnetic resonance cholangiopancreatography · Cholecystectomy · Endoscopic retrograde cholangiopancreatography · Cholestasis · Liver transplantation

Introduction

Biliary diseases in children, although infrequent, can be difficult to diagnose and require varied management. This situation is complicated by the fact that benign and serious disease can often present with similar symptoms. Thus, correct diagnosis of biliary disease in children is essential so that the appropriate treatment modality can be chosen. Diseases such as biliary atresia, Alagille syndrome, and choledochal cysts, although uncommon, require accurate diagnosis and quick treatment. In contrast, benign biliary diseases, such as cholelithiasis and biliary dyskinesia, require accurate diagnosis so that treatment can alleviate associated symptoms.

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Biliary Atresia

Biliary atresia (BA) is an obstructive condition in which all or parts of the extra hepatic bile ducts are absent. The etiology of BA is currently under investigation; however, the result is a process of obliteration of the biliary drainage system. Although the diagnosis of biliary atresia is relatively uncommon, occurring in 1 in 10,000 to 1 in 15,000 live births, it is the leading cause of death from liver failure and the leading indication for liver transplantation in children. Fifty percent of all cases of liver transplantation in children are for BA [1]. Early diagnosis and treatment are essential to re-establish biliary flow and limit cholestatic hepatic injury. In the 1960s, Dr. Kasai introduced a novel surgical intervention for this once uniformly fatal disease. The Kasai hepatoportoenterostomy is the current standard for management of BA worldwide.

Two major forms of biliary atresia have been described: embryonic and perinatal. The embryonic type accounts for 10% to 20% and is associated with other congenital anomalies, including preduodenal portal vein, intestinal malrotation, situs inversus, cardiac defects, and polysplenia. This form of BA is thought to stem from a developmental

defect during differentiation of the hepatic diverticulum. The perinatal type accounts for the majority of cases. In this type, defects occur later in gestation and are generally associated with a progressive obstruction of the biliary tree.

Pathogenesis

Despite extensive interest and numerous investigations, the cause of BA is still largely unknown. Uncertainty is propagated by the fact that BA is often diagnosed late in the disease process. In perinatal BA, causes such as viral infection, genetic mutation, and immunologically mediated inflammation have all been suggested [2]. It is apparent that BA is a multifactorial disease that is uniformly characterized by inflammation and subsequent fibrosis of the biliary tree. The timing of liver injury was recently described by Makin et al. [3••] as occurring primarily after birth, as they found three patients diagnosed with biliary atresia who had normal-appearing liver parenchyma at birth.

Bezerra [4] described five possible etiologies that could be causative of BA: 1) morphogenesis of the biliary tract, 2) defect in prenatal/fetal circulation, 3) environmental toxin exposure, 4) viral infection, and 5) immunologic/inflammatory causes. They explored inflammatory-mediated destruction using a model of BA. In this study, they conclude that an interferon (IFN)-γ–mediated inflammatory pathway is associated with ductal destruction. Other studies have suggested immune-mediated mechanisms as well as viral illnesses that can be responsible for the progressive fibrosis of the biliary tree that is seen in perinatal BA. Regardless of the underlying etiology, BA is uniformly characterized microscopically by inflammatory changes in the biliary tree and fibrotic liver parenchyma due to chronic cholestasis. Untreated, this will lead to cirrhosis and liver failure.

Diagnosis

The diagnosis of BA is difficult to confirm because of numerous physiologic causes of jaundice in the early neonatal period. Untreated BA leads to hepatic failure and its associated complications, and is uniformly fatal. The life span of patients with untreated BA has been shown to be 19 months [5], with less than 10% 3-year survival in untreated patients. Because the outcome from surgery is directly related to timing of intervention, early diagnosis of BA is essential. Specifically, surgery prior to 2 months of age is associated with better outcomes. The 10-year survival rate of patients who are diagnosed and treated prior to 60 days of age is 73% versus 11% in those diagnosed and treated after 90 days of age [6]. Given the correlation of mortality with timing of diagnosis, early diagnosis and treatment are crucial.

BA is only one of many causes of cholestasis in the neonatal period. Common findings of neonatal cholestasis from varied causes include jaundice, hepatomegaly, splenomegaly and acholic stools. Unfortunately, many of these disease processes share similar clinical presentations [7••]. However, unlike most other causes, outcomes in BA are dependent upon speedy diagnosis and intervention. Thus, clinical suspicion and differentiation of BA from other causes of neonatal cholestasis is critical at an early age.

Impaired drainage of bile in BA results in a direct hyperbilirubinemia and subsequent jaundice. However, jaundice is also a prevalent finding in physiologically normal infants as well as in numerous other diseases. It is present in 15% of newborns at 2 weeks of age, and 2% to 6% of infants at 4 weeks, most often from benign processes [8]. Jaundice in an infant after the age of 2 weeks should raise suspicion of the possibility of BA.

The presence of acholic stools in any child is a cardinal sign of possible underlying hepatobiliary disease and demands further clinical investigation. The presence of dark brown urine will coincide with hepatic insufficiency in BA. Growth retardation due to gradual malabsorption of fat-soluble vitamins will eventually be present in patients with BA. Given the prevalence of physiologic jaundice in newborns, an effective mass-screening tool for BA in infants would be valuable. Objective evaluation of stool color in jaundiced infants may help with early detection of BA. Screening with stool color cards in Japan has been effective for identifying infants with BA [9]. In Taiwan, where a nationalized stool color card screening program has been implemented, 58.6% of infants with BA received the Kasai procedure prior to 60 days of age, compared to 23% prior to implementation of screening with the stool color card [6]. As a result, the stool color card is included in a national children's health booklet that is distributed to the caretakers of every neonate in Taiwan at birth.

Although clinical features help to secure the diagnosis of BA, numerous imaging modalities have been used to assist in the diagnostic process. Ultrasound is a simple and noninvasive measure to evaluate hepatobiliary anatomy, and should be instituted first. Common bile duct dilatation is never present in BA. The gallbladder is absent or atretic in 25% of cases of biliary atresia [10]. Presence of a triangular cord sign (hyperechoic triangular area in the porta hepatis that corresponds with the fibrous remnant of the hepatic duct) is 80% sensitive and 98% specific for BA [11]. Hepatobiliary scintigraphy is also a useful tool in diagnosing BA. With BA, there will be a lack of excretion into the intestines on the 24-hour delayed images. Percutaneous transhepatic cholangiography (PTCA), though technically difficult, is used at some institutions to help identify the biliary tree anatomy. Using PTCA, the normal common bile duct should measure less than 1 mm in

neonates, and less than 2 mm in infants younger than 1 year.

Management

Management of BA centers on diversion of bile around obstructed extrahepatic bile ducts. First described by Kasai in 1959, the hepaticoportoenterostomy has provided hope for what was once a uniformly fatal disease. This procedure remains the mainstay of treatment and is performed in more than 90% of infants with BA. Numerous studies have stated that early hepatoportoenterostomy is a key factor in transplant-free survival, resolution of jaundice, and overall survival [12••].

Although the Kasai procedure provides hope for infants with BA, it is not without complications. Cholangitis is the most frequent complication within the first 2 years postoperatively and has been reported in up to 55% of patients postoperatively. To lower this risk, some clinicians prescribe prophylactic antibiotics in the first year postoperatively [13]. Portal hypertension is another common complication thought to be related to intrahepatic damage from inflammation and ongoing fibrosis. Other complications can include intrahepatic cysts, hepatopulmonary syndrome, development of hepatic malignancy, and fat malabsorption [2].

In general, the return of biliary flow after Kasai portoenterostomy will result in resolution of acholic stools and jaundice. Return of acholic stools or jaundice is worrisome for recurrence of biliary stasis, presumably from inflammatory changes and subsequent fibrosis in the remaining biliary structures. Normal serum bilirubin should be achieved by 3 months postoperatively. At 3 months postoperatively, serum bilirubin below 2 mg/dL is associated with low likelihood to require hepatic transplant within 2 years, whereas serum bilirubin at or above 6 mg/dL is associated with higher likelihood of failure and subsequent need for hepatic transplantation [14].

Outcomes

Since the 1970s, studies evaluating the long-term outcomes of patients after the Kasai procedure have shown mixed results. Studies in France and Japan have focused on surgical experience and outcome. In both countries, better outcomes are seen in facilities that perform more than five Kasai operations per year compared to facilities that perform less than five annually [13]. These findings have prompted the formation of the Biliary Atresia Research Consortium (BARC) in the United States. Currently, 12 BARC-affiliated facilities in the United States contribute to research and surgical innovation, and focus on biliary atresia.

Shneider et al. [14] reported some of the first data from the BARC hospitals in 2005. They followed 104 patients diagnosed with BA who received portoenterostomy at a BARC-participating facility. At 24 months of age, 58 patients were alive with their native liver, 42 patients required liver transplantation, and four patients died of congenital heart disease. Elevated bilirubin levels at 3 months postoperatively were associated with worse outcomes and increased likelihood to require liver transplantation within 2 years [13]. These data are consistent with data from other nations in which specialty centers are beginning to be used for surgical intervention.

Although short-term data are important to help define prognostic indicators, long-term outcomes are becoming evident. In 2009, Shinkai et al. [15••] reviewed 80 patients who underwent the Kasai procedure between 1970 and 1986 at the Kenagawa Children's Medical Center in Yokohama, Japan. The mortality at 20 years after Kasai operation was 50%, although many of these patients died prior to the initiation of liver transplantation programs in Japan. The 5-, 10-, and 20-year transplant-free survival rates of the survivors were 63%, 54%, and 44%, respectively [15••]. Although transplant-free survival is important, hepatic function and quality of life measures varied tremendously in those who had not required transplant at the time of this publication. These investigators were also able to demonstrate that age less than 70 days at hepatoportoenterostomy is significantly associated with long-term transplant-free survival.

New Developments

Evidence continues to suggest that early diagnosis and surgical intervention for BA is associated with longer transplant-free time as well as better overall mortality. However, Raval et al. [12••] reported in 2010 that the mean age at which portoenterostomy is performed in the United States—65.5 days of life—has not improved in the past 10 years. In particular, they noted that, although the BARC was established in 2002 (currently with 12 participating centers), only 10.9% of patients receiving hepatoportoenterostomy received them at a BARC facility. Those patients had surgery done at an earlier age, although it is uncertain whether this factor improved outcome. Data from France, the United Kingdom, and Japan suggest that surgery for BA performed at specialized centers is associated with better outcomes. Given these findings, it appears apparent that continuing to develop specialized centers for the care and treatment of BA could possibly be associated with better outcomes in the future. Because early intervention by a specialized center is still dependent on early referral, better screening (eg, home stool cards) is needed to ensure timely surgical intervention.

The use of steroids following surgery for BA has been questioned for several years. The observation that BA is characterized by histopathologic findings of inflammatory changes led to speculation that the immunosuppressant and choleretic effects of steroids may help with postoperative outcomes of the Kasai procedure. Although this has been studied extensively for the past 20 years, it continues to be a significant debate in treatment for BA. It has been shown that steroids can contribute to a rapid decrease in postoperative bilirubin. However, overall transplant-free time and incidence of cholangitis has not significantly improved [16, 17]. A recent retrospective analysis by Lao et al. [18••] suggests there is no significant reduction in incidence of cholangitis or mortality, although postoperative steroids were associated with shorter hospital stays. To help answer this question, the BARC is currently enrolling more patients in a double-blind, placebo-controlled trial to analyze the effects of corticosteroids on serum bilirubin and mortality in BA.

Ursodeoxycholic acid (UDCA) has been used to augment treatment for cholestatic disease secondary to its cytoprotective effect on hepatocytes and its ability to increase hepatic clearance of toxic endogenous bile acids. UDCA has also been shown, in vitro, to decrease proliferation of mononuclear cells and cytokine production. Willot et al. [19] studied the effects of UDCA on liver function in patients following Kasai portoenterostomy. In this study, 16 patients were treated with UDCA postoperatively. All patients included in the study then had their UDCA stopped and chemical mediators of liver injury were monitored, including aspartate aminotransferase, total bilirubin, alanine aminotransferase, and γ-glutamyl transpeptidase. In all 16 patients, elevations of indicators of liver injury and malfunction were seen. The authors concluded that UDCA might be a beneficial treatment to prolong native liver survival and delay liver transplantation in patients after undergoing Kasai [19]. Randomized, controlled trials are needed to evaluate UDCA in the future. Despite the lack of evidence, 75% to 80% of patients treated at BARC-participating centers receive UDCA in the first 1 to 3 months after the Kasai procedure [14].

Alagille Syndrome

Described in 1967, Alagille syndrome (AGS) is a multisystem, autosomal dominant syndrome of cholestasis with variable expressivity. It affects 1 in 30,000 live births [20••]. The syndrome is characterized by a paucity of interlobular bile ducts with other associated features including cholestasis (present in 96% of patients), cardiac anomalies (97%), butterfly vertebrae (51%), posterior embryotoxin of the eye (78%), and dysmorphic facies (96%) [21]. The dysmorphic facial features of AGS are described as a broad nasal bridge, triangular facies, and deep-set eyes. Renal anomalies, both functional and structural, and neurovascular accidents are less common (15%), but can be associated with AGS. AGS is thought to be caused by a deletion or mutation of the *JAG1* cell surface protein sequence on the short arm of chromosome 20. *JAG1* serves as the ligand for the Notch transmembrane receptor, which is a key signaling molecule in many cell types in dictating cell fate [22].

Clinical suspicion should drive the initial workup and evaluation of suspected AGS. The presence of three of five of the above-mentioned major clinical findings is highly suspicious for AGS. Thus, ophthalmologic examination, echocardiogram, and imaging of the vertebrae are all useful in ascertaining the diagnosis. As with most infants with suspicion of cholestatic disease, initial evaluation of suspected AGS includes liver function tests as well as prothrombin time and fat-soluble vitamin levels. Given that BA must be considered in an infant with cholestasis, an ultrasound is used in the diagnosis, although there are no specific findings related to AGS that can be visualized on ultrasound. Hepatobiliary scintigraphy and intraoperative cholangiogram may help to delineate AGS from BA. However, no evidence of tracer excretion from the liver was found in 61% of patients with a diagnosis of AGS in one study, which complicates the delineation [21]. In these patients, cholangiogram, either percutaneous or intraoperative, may be useful. Hypoplasia of the extrahepatic biliary tree was also described in some patients with AGS [21]. In such cases, liver biopsy can be performed to ascertain the proper diagnosis, because bile duct paucity was documented on liver biopsy in 85% of all patients with AGS. However, in younger infants (< 6 months), bile duct paucity on biopsy was described to be present in only 60% of patients with a diagnosis of AGS [21].

The advent of genetic testing for AGS has led to an increase in diagnosis. Genetic evaluation should be ascertained in any patient in whom clinical suspicion for AGS is present. Deletion or mutation of the *JAG1* gene on the short arm of chromosome 20 is present in 60% to 70% of patients with AGS [23].

Management of AGS focuses on treatment of the individual components of the disease. Cholestasis is most commonly treated with choleretics, most commonly ursodiol. Synthetic liver function is rarely affected in AGS, unless it progresses to end-stage liver disease. AGS can be associated with a debilitating pruritus from hyperbilirubinemia. Symptomatic treatment is provided with antihistamines, sedatives, and rifampin. In refractory pruritus, partial biliary diversion can be performed. In many children, the pruritus resolves after the first decade of life. Cardiac disease in AGS can be variable, and management is focused on a lesion-specific basis.

Because AGS can be associated with nutritional deficiencies and developmental delays, aggressive nutritional therapy and fat-soluble vitamin supplementation should be provided. Surgical intervention is not recommended for AGS at this time. In fact, surgical intervention has been associated with worse hepatic outcome in patients with a diagnosis of AGS [24••]. Because of the similarities in diagnostic findings between BA and AGS, every attempt should be made to ascertain the diagnosis before proceeding with portoenterostomy in children with cholestasis to avoid surgical intervention for presumed BA on patients with an actual diagnosis of AGS.

End-stage liver disease occurs in 20% of patients with AGS and is secondary to chronic cholestasis [25]. Liver transplantation is indicated in patients with end-stage liver disease or intractable failure to thrive despite enteric nutritional support [26]. Prognosis in AGS has been shown to be associated with the presence of complex heart disease: intracardiac disease in patients with AGS is associated with higher mortality [21]. Twenty-year survival for all patients with AGS has been described as 75%. In those patients who did not require transplantation, the 20-year survival is 80%, compared to 60% in those who required transplantation [21].

Choledochal Cysts

Epidemiology

Choledochal cysts are a rare medical condition, occurring in 1 in 100,000 to 150,000 live births worldwide. However, there appears to be an unexplained higher incidence of 1 in 1000 live births in Asian populations [27, 28]. Typically, choledochal cysts present with jaundice, abdominal pain, and a right upper quadrant mass in older children and adults. However, younger children rarely present with all three components of the triad. There is a female predominance with a female to male ratio of 3.5 to 1 [28]. Choledochal cysts commonly present prior to the age of 2, although they can be diagnosed antenatally.

Classifications

Choledochal cysts are currently classified by the Todani modification of the Alonzo-Lej classification into one of five categories depending on number of cysts, intrahepatic versus extrahepatic location, and type of bile duct dilatation. Type I cysts have cystic dilatation of the common bile duct alone. Type II cysts have a cystic diverticulum of the extrahepatic common bile duct. Type III choledochal cysts, commonly referred to as choledochoceles, have dilatation of the distal common bile duct within the wall of the duodenum and involve the ampulla of Vater. Type IV choledochal cysts have multiple cystic dilatations of the bile ducts. These are further classified into subtypes: Type IVA cysts involve multiple intra- and extrahepatic ductal dilatations, whereas type IVB cysts involve multiple extrahepatic common bile duct dilatations. Type V choledochal cysts, referred to as Caroli's disease, consist of multiple intrahepatic dilations of the bile ducts [28]. Although five subtypes of choledochal cysts have been described, 80% to 90% of diagnosed choledochal cysts will fall into the type I classification.

Pathogenesis

Several etiologies of choledochal cysts have been hypothesized. One proposed etiology is from an abnormal pancreaticobiliary junction proximal to the ampulla of Vater resulting in an abnormally long common channel. This may allow pancreatic enzymes to reflux into the common bile duct, and cause inflammation and subsequent deterioration of the duct wall, with resultant ductal dilation. This theory is supported by evidence of higher levels of pancreatic amylase found in choledochal cysts, suggestive of reflux of pancreatic fluid. Critics of this theory argue other etiologies because only 50% to 80% of choledochal cysts contain an abnormal pancreaticobiliary ductal connection. Reports have shown that an abnormal pancreaticobiliary ductal junction is more commonly found in children than in adult patients with choledochal cysts [29••]. The length of a long common channel is loosely defined in the literature as between 10 mm and 40 mm [28].

Another theory regarding the pathogenesis of choledochal cysts is that they are congenital in nature because of ductal obstruction with subsequent dilatation of the common bile duct system. Distal obstruction may be due to sphincter of Oddi dysfunction or aganglionosis such as that which occurs in Hirschsprung's disease. A decrease in elastin in infants prior to the age of 1 year and an increase in biliary tree pressure from distal obstruction could lead to proximal dilatation.

Clinical Presentation

Eighty percent of patients with choledochal cysts will present before the age of 10 years [29••]. The classic triad of abdominal pain, jaundice, and a palpable abdominal mass is present in less than 20% of patients with choledochal cysts [30]. More commonly, patients will present with fevers, abdominal pain, nausea, and vomiting. A palpable abdominal mass will more often be seen in children [31]. In one study, 53% of children with choledochal cyst presented with an abdominal mass, compared to only 21% of adults [29••]. In most cases,

presenting symptoms are due to secondary complications of choledochal cysts, such as ascending cholangitis, biliary stasis, inflammation, and pancreatitis. Thus, clinical suspicion must be raised in any pediatric patient with recurrent bouts of pancreatitis or other symptoms consistent with biliary stasis. Recurrent infections and obstruction with choledochal cysts can lead to secondary biliary cirrhosis, which may lead to portal hypertension with splenomegaly and gastrointestinal bleeding.

Imaging

Abdominal ultrasound, with a sensitivity of 71% to 97%, remains the best choice for imaging in patients who are suspected of having a choledochal cyst [30]. Most choledochal cystic lesions are able to be seen by routine ultrasonography [32]. Information obtained should include the diameter of the common bile duct as well as the degree of intrahepatic dilation. Visualization of a cystic mass on ultrasound must be confirmed to be within the biliary tree because of the frequency of other cystic abdominal structures, including pancreatic pseudocysts. Although CT scan and endoscopic retrograde cholangiopancreatography (ERCP) were useful in the past for diagnosis of choledochal cyst, they are quickly being replaced by MRI and magnetic resonance cholangiopancreatography (MRCP) as the diagnostic test of choice for identifying surrounding anatomy.

A technetium-99 m hepatic iminodiacetic acid (HIDA) scan is helpful to view the continuity of bile ducts. However, visualization of the intrahepatic ductal system is not optimal and makes this modality inadequate for type IV or V choledochal cysts. HIDA scans are useful to delineate choledochal cysts from the more urgent diagnosis of biliary atresia in the neonatal period. These two diseases can be differentiated by visualization of contrast in the small bowel, which will be seen with a choledochal cyst, but not with biliary atresia.

Cholangiography has long been the gold-standard imaging modality for diagnosis and operative planning for choledochal cyst, because it enabled complete and detailed visualization of the biliary tree [30]. However, given the development of other imaging modalities, cholangiography (percutaneous, endoscopic, or intraoperative) has become less necessary. Choledochal cysts have an increased risk of cholangitis and pancreatitis, which may be exacerbated by the administration of contrast and manipulation of the ampulla. ERCP requires anesthesia, whereas other imaging modalities that might elicit the same information do not.

MRCP (rather than ERCP) has been used increasingly as an imaging modality for visualization of the biliary tree. MRCP is favorable to ERCP because it avoids ionizing radiation exposure and is not associated with increased risk of cholangitis or pancreatitis. MRCP is limited by its inability to delineate subtle findings in the biliary tree, especially in children less than 3 years of age. In 2002, Kim et al. [33] revealed that MRCP was able to accurately show aberrant pancreaticobiliary union in 60% of patients prior to intraoperative cholangiography. Park et al. [34] in 2005 revealed that MRCP was able to detect choledochal cysts in 96% of their patient population, and provided diagnostic images to determine the type of cystic lesion present in those patients. Given its ability to provide adequate diagnostic imaging of choledochal cysts while also minimizing risk, MRCP will likely replace ERCP for diagnosis of most choledochal cysts.

Abdominal ultrasound remains the initial imaging modality of choice in patients suspected of having a choledochal cyst. If further imaging is needed to delineate anatomy, cholangiography in the form of MRCP is recommended, if possible. HIDA scan is useful in the neonatal patient to differentiate choledochal cyst disease from biliary atresia.

Treatment

Because the risk of malignancy with retained choledochal cysts is high, excision of the cyst is the recommended treatment. In the 1950s, internal drainage with cystenterostomy provided good relief of symptoms. This practice was abandoned in the mid 1980s because enteric reflux into the cyst commonly caused cholangitis; furthermore, evidence began to suggest an increased rate of malignancy in patients with retained choledochal cysts. Subsequently, there is more evidence that retention of the cyst mucosal layer increases the risk of development of biliary carcinoma. Total cyst excision with hepaticoenterostomy is now the standard treatment for choledochal cyst disease. By creating a roux-en-Y hepaticojejunostomy for biliary drainage, the biliary tree is isolated from the pancreatic duct and the pancreatic duct drains into the native duodenum. This eliminates pancreatic reflux into the biliary tree, thought to be the etiology of choledochal cyst disease. The success rate of hepaticojejunostomy was reported as high as 92% in some studies [35]. The technical challenge of complete cyst excision can be made more difficult if chronic inflammation is present, and may risk injury to the underlying portal vein. A safe alternative is to perform partial cyst excision with mucosectomy when inflammation and adhesions make a complete cystectomy hazardous.

Regardless of previous surgery or other comorbidities, surgical intervention should always include cholecystectomy and cyst excision in its entirety for type I, II, and IV cysts [31, 36]. Although some surgeons advocate hepaticoduodenostomy because it appears more physiologic, this procedure has been associated with an increased complication rate (42%), including increased risk of biliary gastric reflux with resultant gastritis and esophagitis [37]. Because

of these complications, Shimotakahara et al. [37] advise against performing hepaticoduodenostomy in children with choledochal cyst. Complications of hepaticojejunostomy include cholangitis, most commonly in the immediate perioperative setting. Bowel obstruction, chronic abdominal pain, and biliary cirrhosis can occur as late complications. Overall, several studies report that long-term complications from complete cyst excision are rare. Mortality in the pediatric population from hepaticojejunostomy is low—0% in some studies [29••]. Management of type III cysts involves unroofing the cyst, via open duodenotomy or more recently by ERCP, to allow internal drainage into the duodenum. Hepaticojejunostomy is not effective in type V choledochal cysts (Caroli's disease) because of the intrahepatic nature of the disease; management is still controversial, although many surgeons advocate partial hepatectomy if lesions are isolated to one lobe [31]. Other surgeons have advocated roux-en-Y cholangiojejunostomy, with placement of transhepatic stents in some cases [31]. Extensive disease may require hepatic transplantation. Regardless of the surgical intervention chosen for choledochal cyst disease, long-term follow-up is required because of continued risk for the development of malignancy in the intrapancreatic common bile duct or the hepaticojejunostomy anastomotic site.

Outcomes

Choledochal cysts are known be at risk for malignant transformation. The reason for this is not entirely clear, although cellular dysplasia as a result of chronic inflammation, recurrent infections, or the presence of pancreatic enzymes have all been suggested. The risk of malignancy has been described as high as 75% in patients by the age of 70 if the cyst is not excised. Rates of biliary tree carcinoma after cyst excision have been shown to be 0.70% in long-term follow-up, which further justifies cyst excision [38]. Adenocarcinoma is responsible for 73% to 84% of tumors.

Gallbladder Disease

Until recently, cholelithiasis in the pediatric population was almost uniformly attributed to an underlying disease process, such as a hemolytic disease or parenteral nutrition administration. However, since the 1960s, the number cholecystectomies in children has steadily increased, particularly with the application of laparoscopy to children and improvement in diagnostic modalities such as ultrasound in the 1980s. These factors have allowed for more expedient diagnosis and treatment of cholelithiasis [39]. However, gallbladder disease in general tends to be more prevalent in the adult population when compared to the pediatric population. Similarly, the diagnosis of gallbladder disease in children is more difficult because the descriptions of symptoms tend to be vague, clouding the clinician's ability to diagnose biliary disease [40].

Biliary Dyskinesia

Gallbladder dyskinesia is characterized by an impairment or irregularity in emptying of the gallbladder, and must be considered in any pediatric patient with chronic abdominal pain. The diagnosis is most common between the ages of 14 and 16 [40–42]. Because of the wide differential diagnosis in patients with abdominal pain, patients with gallbladder dyskinesia have often suffered with symptoms for a long time and have undergone numerous studies with negative results [42]. Biliary dyskinesia in children presents with similar symptoms to those of gallstone disease, including right upper quadrant pain, fatty food intolerance, nausea, vomiting, and abdominal pain [41]. The diagnosis of gallbladder dyskinesia is most often made via cholecystokinin–diisopropyl iminodiacetic acid (CCK-DISIDA) scanning with a gallbladder ejection fraction of less than 35% or pain with administration of CCK, which are suggestive of dyskinesia in the absence of cholelithiasis.

The treatment for gallbladder dyskinesia is cholecystectomy. Kaye et al. [42] showed that 77.3% of patients who were diagnosed with gallbladder dyskinesia, and who had pain with CCK-DISIDA scan, had resolution of symptoms after laparoscopic cholecystectomy. Similarly, Hofeldt et al. [40] reported a 93% likelihood of resolution of symptoms in children with a known ejection fraction of less than 15% and associated right upper quadrant pain. The results of this study and numerous others suggest that laparoscopic cholecystectomy is the standard treatment for children with gallbladder dyskinesia when the diagnosis has been confirmed and other etiologies have been ruled out as the cause of their symptoms.

Cholelithiasis

Cholelithiasis is a rare disease in children. Less than 0.2% of patients with gallstones are under the age of 15 years [43]. The most common causes of cholelithiasis are hemolytic diseases such as sickle cell anemia, thalassemia, and hereditary spherocytosis. Nonhemolytic causes of cholelithiasis include parenteral nutrition administration, cystic fibrosis, and metabolic disorders. The incidence of cholelithiasis in patients with sickle cell disease has been reported as high as 50% by the age of 18 years [44].

Cholelithiasis can be complicated by cholecystitis, pancreatitis, and biliary colic. However, many children with cholelithiasis are asymptomatic. Bogue et al. [45]

reported that clinically silent cholelithiasis can be managed safely via conservative management, as in adults. However, the presence of complications is an indication for laparoscopic cholecystectomy. In their study, they suggest that cholelithiasis from hemolytic disease is associated with a higher risk of complications [45]. Laparoscopic cholecystectomy is safe and effective for treatment of symptomatic cholelithiasis in children.

Conclusions

Biliary disease in children can present numerous challenges for diagnosis and treatment. Because of the mortality associated with pediatric biliary diseases such as BA and choledochal cysts, accurate diagnosis and appropriate treatment are essential. Although the etiology of biliary disease in children is still being investigated, advances are being made in diagnosis, medical treatment, and surgical intervention. Careful attention to detail during diagnostic workup and early intervention are essential.

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