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Diseases of bile duct in children

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Abstract

Several diseases originate from bile duct pathology. Despite studies on these diseases, certain etiologies of some of them still cannot be concluded. The most common disease of the bile duct in newborns is biliary atresia, whose prognosis varies according to the age of surgical correction. Other diseases such as Alagille syndrome, inspissated bile duct syndrome, and choledochal cysts are also time-sensitive because they can cause severe liver damage due to obstruction. The majority of these diseases present with cholestatic jaundice in the newborn or infant period, which is quite difficult to differentiate regarding clinical acumen and initial investigations. Intraoperative cholangiography is potentially necessary to make an accurate diagnosis, and further treatment will be performed synchronously or planned as findings suggest. This article provides a concise review of bile duct diseases, with interesting cases.

Key Words: Bile duct; Cholestasis; Biliary atresia; Biliary hypoplasia; Biliary imaging; Inspissated bile syndrome; Choledochal cyst

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Core Tip: Bile duct diseases are rare conditions in children but are mostly pathologic and require timely investigations and management. Biliary atresia (BA) is a common cause of biliary cirrhosis, and affected children with delayed diagnosis require liver transplantation. Early detection of BA using stool color charts or proposed biomarkers has been integrated into the management of infants with cholestasis in many countries. Extrahepatic biliary obstruction caused by stones and choledochal cysts can be easily diagnosed by abdominal ultrasonography and treated by surgical resection. Nowadays, genetic analysis plays a vital role in many bile duct diseases, such as Alagille syndrome. In addition, advanced endoscopic management can improve treatment outcomes and is less invasive than conventional surgical therapy.

INTRODUCTION

Bile duct diseases can have a congenital or acquired etiology. The majority of bile duct diseases are present in infants with progressive jaundice. Imaging is the mainstay of investigation, and other more invasive procedures such as intraoperative cholangiography and liver biopsy may be needed to confirm the diagnosis. Genetic analysis has recently been helpful for the diagnosis of particular bile duct diseases such as Alagille syndrome (AGS). In addition, genetic predisposition is well described in biliary atresia (BA); however, more informative research is required in this field. This review will focus on bile duct diseases that are mainly present during the infant period, including BA, bile duct hypoplasia, inspissated bile plug, and choledochal cysts (CDCs).

EPIDEMIOLOGY

The worldwide incidence of bile duct disease varies among countries. BA and CDCs are considered more common in Asia than in Europe and America. The prevalence of BA is approximately 1:5000 in Taiwan and 1:20000 in Europe and America[1]. The prevalence of CDCs is 1:1000 live births in Japan and 1:13500 live births in America, whereas it is only 1:100000-500000 live births in Western countries[2]. For AGS, initial estimates suggest that AGS occurs in 1 per 70000 live births; however, with molecular testing, it is likely closer to 1 per 30000 live births (117). In children, the incidence of cholelithiasis ranges from 0.13% to 0.22%[3]. Hemolysis, cystic fibrosis, prolonged fasting period and ceftriaxone use were associated conditions that increased the incidence of cholelithiasis. The link between genetic predisposition and stone formation has been described in reported cases and needs further study.

BA

BA is the most common bile duct disease in infants and generally requires timely surgical management for excellent outcomes. According to the proposed pathogenesis, BA can be classified into three clinical variants[4]. The isolated or perinatal form

accounts for 80%-90% of BA cases. Casual factors include genetic predisposition[5,6], ischemic process[7], environment[8], and infection[9-11]. Cytomegalovirus (CMV) is the most common pathogen that may be associated with BA[11-13]. Zhao *et al*[14] reported that up to 30% of BA cases in China might be related to CMV based on findings in liver histopathology. This finding suggests the potential role of perinatal CMV infection in BA development, from a complex autoimmune process that involves transient viral infection of choanocytes, activating the innate immune system and adaptive T-cell proliferation. In addition, CMV may trigger self-damage, leading to persistent proinflammatory immune responses driven by various immune cells[15,16]. Compared with CMV immunoglobulin (Ig)M-negative controls, CMV IgM-positive infants have worse outcomes, with reduced jaundice clearance, lower native liver survival (NLS), and increased mortality[17]. Nonetheless, no universal consensus has been established on incorporating CMV eradication into BA adjunctive treatment. Genetic predisposition, possibly non-Mendelian, may be involved in BA development. Studies have linked genes such as ADD3, XPNPEP1, and GPC-1 to isolated BA[5]. GPC-1 plays a role in biliary physiology and inflammatory mediators[18]. The overlap between isolated BA and other neonatal cholestasis syndromes such as AGS[19] and progressive familial intrahepatic cholestasis[20] has been reported.

Syndromic or embryonic form is known as BA splenic malformation (BASM) syndrome, which is more common in Europe and America (10%-15%)[21,22] but rare in China and Japan[23,24]. BASM is characterized by distinct visceral anomalies, including polyphemid, situs inversus, preduodenal portal vein, and absence of the intrahepatic vena cava (Figure 1). Cardiac anomalies are also present in approximately half of the cases. BASM likely stems from embryonic defects, possibly related to genetic mutations, including PKD1L1, CFC1, NODAL, FOXA2, and ZIC3, *e.g.*,[25] or maternal diabetes and other first-trimester factors[12]. Other syndromes that might be linked with BA include cat-eye syndrome or aneuploidy of chromosome 22[26], Kabuki syndrome[27], Zimmermann-Laband syndrome, Kartagener syndrome, Hirschsprung disease, and various isolated anomalies such as gastrointestinal atresia and cleft palate[12].

Cystic BA (CBA) is characterized by the cystic dilatation of the extrahepatic bile ducts and fibrosing obstruction of the duct segments. CBA must be differentiated from CDCs, which can be seen in prenatal ultrasonography but has different clinical courses[28]. In infants, CBA tended to present at a younger age. Jaundice and acholic stools may manifest shortly after birth or following a variable period. In a comprehensive review of BA cases, CBA was observed in approximately 8% of patients[29]. Operative cholangiography is essential for diagnosing an infant with jaundice and postnatally confirmed subhepatic cysts. In CBA, cholangiography may reveal an abnormal, tenuous connection with the intrahepatic ducts or ductules, which is often described as "cloud-like"[30]. This suggests an onset beyond 12 wk of gestation, possibly related to an ischemic event affecting the distal extrahepatic duct[12]. Experimental models have reproduced key CBA features by ligating the common bile duct (CBD) in fetal lambs or the hepatic artery in fetal rabbits, resulting in cystic extrahepatic changes and impaired intrahepatic bile ducts[31,32]. These studies have suggested that ischemia and altered angiogenesis may play a role in the pathogenesis of CBA and other BA variants. Most CBA cases require radical resection and wide portoenterostomy. Compared with other BA variants, CBA generally has a better long-term prognosis; however, some cases may still require liver transplantation (LT) during adulthood[33].

According to the Japanese Society of Pediatric Surgeons, it is classified into three main types: Type 1, CBD atresia; type 2, common hepatic duct atresia; and type 3, right and left hepatic duct atresia. The classification also considers variations in the gallbladder/CBD and hilar plate. When the proximal biliary tree is absent, the condition is called biliary agenesis. "Correctable" lesion, where the distal CBD is atretic but a portion of the extrahepatic duct connects to the intrahepatic ducts, allows direct drainage *via* Roux-en-Y anastomosis. The most common lesion (75%-85%) involves complete duct obliteration throughout the porta hepatis (type 3), which is often considered "noncorrectable" atresia. In these cases, residual bile duct remnants may be present within the fibrous tissue. The Kasai portoenterostomy (KPE) attempts biliary drainage by excising the obliterated extrahepatic ducts and reconstructing the

transected porta hepatis to the bowel mucosa in Roux-en-Y hepatoportoenterostomy (76) (Figure 2).

Clinical signs and symptoms

Typical presentations of BA include conjugated hyperbilirubinemia and acholic stools at birth for the embryonic form but at 3-4 wk of life for other forms. BA could rapidly progress to hepatomegaly, failure to thrive, pruritus, and coagulopathy within a few months because the affected infants are typically healthy and born at term. Delayed diagnosis is common; hence, early screening for timely surgical management is advocated.

Newborn screening for BA

Timely recognition of BA, ideally by a 2-wk well-baby visit, is paramount for optimal intervention. The Children's Liver Foundation[34] in the United Kingdom and the American Academy of Pediatrics guidelines[35] introduced a screening program aimed at identifying neonatal liver diseases through jaundice assessment (Table 1).

"Yellow alert" educational campaign

This campaign was initiated in the United Kingdom in 1993 at King's College Hospital and aimed to ensure bilirubin testing in all babies with persistent jaundice 2 wk after birth. However, relying solely on jaundice detection poses challenges. Infants with BA may not appear jaundiced during the initial well visits because their bilirubin levels can still be below the visual threshold in the first few weeks. In addition, many infants may appear jaundiced because of nonhepatic causes, such as physiologic jaundice or breast milk jaundice. This campaign, which is ongoing and developed by the United Kingdom Children's Liver Disease Foundation, focuses on raising awareness of jaundice in children. They have also introduced the "Yellow Alert App" to further support this cause.

Stool color card (SCC) program

Another screening approach uses a stool color card (SCC) program[36]. In 1994, Matsui and Ishikawa[37] introduced a seven-color panel SCC to the Maternal and Child Health Handbook distributed to pregnant women in the Tochigi Prefecture in Japan. Parents returned the completed SCC to the physician either before or during the 1-month follow-up. All suspected cases were referred for investigation. Between 1994 and 2001, 313230 newborns underwent screening, and BA was diagnosed in 32 newborns. The average age at KPE was 60 d, marking a significant reduction from 70 d in the history before the SCC program[38]. In 2002, Taiwan introduced an SCC program to improve the early diagnosis of BA[39]. This study examined the 5-year outcomes of BA both before and after the implementation of the SCC program. When comparing the groups before and after SCC implementation, the rate of KPE performed within 60 d significantly increased from 49.4% to 65.7%. Three months after KPE, the jaundice-free rate [total bilirubin (TB) < 2 mg/dL] increased from 34.8% to 60.8%. The 5-year jaundice-free survival rate with native liver increased from 27.3% to 64.3%, and the overall survival rate improved from 55.7% to 89.3%. Screening with SCC is increasingly used in Europe[40-42]. In Switzerland[42], the card has been available for voluntary distribution since 2009. It is provided at birth or during the first appointment at 4 wk of age. If an abnormal stool color is noted, the pediatrician is advised to promptly contact a gastroenterologist. The SCC program has been assessed from 2014 to 2016 in British Columbia[41]. All 126 maternity units received SCC. Of the 87583 live births, 6 cases of BA were identified. The screening program successfully referred three of the six BA cases to specialized care (defined as program screen success). Among the three cases in which the program did not detect BA, two families recognized pale stools and promptly consulted their healthcare providers. However, they were reassured, and no further immediate action was taken. The median age at KPE was 49 (range 42-52) d, whereas for the failure to detect the SCC group, it was 116 (range, 49-184) d. The program demonstrated a sensitivity of 50%, specificity of 99%, positive predictive value (PPV) of 4%, and negative predictive value (NPV) of 99%[41]. Currently, small pilot studies with

SCC have been conducted in various regions, including Brazil, Cairo (Egypt), Shenzhen (China), Northern Portugal, and Lower Saxony (Germany)[43].

Mobile applications

Several centers have developed mobile smartphone applications designed to assist parents and caregivers in identifying abnormal stool color and prompt early referral to specialty care. Notable examples include PoopMD[44], BabyPoop, and Popo□app, each using smartphone cameras and color analyzer software to assess infant stool color. PoopMD, developed at John Hopkins University in the United States and implemented in 2014, demonstrated a sensitivity of 100% and specificity of 89% in detecting acholic stools[44]. It demonstrates precise discrimination between acholic and normal stool colors, showing substantial agreement among users and nearly perfect concordance across two popular smartphones under various ambient light settings. BabyPoop, which was used in Japan in 2016, analyzed data from 54 BA and 100 non-BA stool images to refine its color detection algorithm. It demonstrated 100% sensitivity and specificity in detecting BA within a test set of 40 stool images, including five from BA cases[45] Popo□app®[46], created by an Italian team, employs a color analysis algorithm based on a Japanese seven-stool color photo panel. This was validated by four pediatric subspecialists using 160 stool samples from infants aged < 6 months. It provided a sensitivity of 100% and a specificity of 99%.

Fractionated bilirubin levels

The screening approach involves measuring fractionated bilirubin levels in newborns[47]. In 1998, a United Kingdom study pioneered the use of fractionated bilirubin testing for newborn BA screening. This involved measuring conjugated bilirubin levels in infants aged 4-28 d using additional plasma from routine newborn screening[48]. Subsequently, in a prospective study of 23214 patients with defined bilirubin cutoffs, the testing showed high sensitivity (100%), specificity (99.6%), and PPV (10.3%) for BA detection[49]. This method also identified other conditions such as

AGS, alpha-1-antitrypsin deficiency, and panhypopituitarism. In the United States, recent studies have focused on bilirubin testing within the first 24-48 h of life, recognizing that newborns with BA display high direct or conjugated bilirubin levels from birth. The screening process involves collecting blood for testing from all infants before discharge from the nursery. Infants with high fractionated bilirubin levels were subsequently retested as outpatients during the routine 2-wk well-child visit, and those with persistently high levels underwent further evaluation. This algorithm was assessed in a pilot study of 11636 infants and a larger follow-up study of 123279 infants, resulting in notable improvements in the timing of KPE. This method is now being used in various United States countries, including San Antonio, Salt Lake City, New Orleans, and their surrounding areas. Studies have shown a sensitivity of 100% and a specificity of 99.5%-99.9% in detecting BA cases[48,49]. Nevertheless, some limitations were noted, including variations in direct bilirubin assays, higher positive rates among Black infants, and the need for coordination between nurseries and primary care providers[36].

Laboratory markers

Other laboratory markers such as gamma-glutamyl transferase (GGT) and matrix metalloproteinase-7 (MMP-7)[50,51], which are markers of biliary epithelial injury, have established significance in the diagnosis of BA. Lertudomphonwanit *et al*[51] demonstrated that combining serum MMP-7 with GGT resulted in a high sensitivity of 97% and specificity of 94% for diagnosing BA. Yang *et al*[52] analyzed 54 infants with cholestasis aged < 6 months (22 with BA and 32 with non-BA) in comparison with 41 control infants. They assessed the accuracy of MMP-7 in distinguishing BA from other causes of cholestasis. MMP-7 exhibited outstanding diagnostic accuracy for BA, with an area under the curve of 0.990, a cutoff value of 52.85 ng/mL, a sensitivity of 98.67%, and a specificity of 95%. Rohani *et al*[53] reported a similar finding with a sensitivity of 95.5% and a specificity of 94.5%.

Serum and urine bile acids

A promising screening method under investigation measures BAs in dried blood spots, potentially integrating BA screening with standard newborn metabolic screening[36]. Initial attempts using tandem mass spectrometry did not effectively distinguish between healthy newborns and those with liver disease[54]. However, Zhou *et al*[55] analyzed primary bile acids in dried blood spots from 8 infants with BA, 17 infants with neonatal jaundice, and 292 comparison infants at 3-4 d of life. Taurocholate (TC) levels were significantly higher in BA (0.98 ± 0.62 mmol/L) than in neonatal jaundice (0.47 ± 0.30 mmol/L) and comparison infants (0.43 ± 0.40 mmol/L). The use of a cutoff of 0.63 mmol/L yields a sensitivity of 79.1% and specificity of 62.5%. This suggests that while TC shows promise as a potential newborn screening marker for BA, further evaluation is needed to assess its cost-effectiveness and ability to detect other liver diseases. A recent prospective multicenter study in Japan[56] investigated urinary oxysterol analysis in patients with BA, suggesting that 27-hydroxycholesterol holds promise as a potential marker for distinguishing BA from other causes of neonatal cholestasis. The study included 14 infants with BA, 10 non-BA cholestatic controls, and 10 healthy controls. Among patients with BA, urinary 27-hydroxycholesterol levels were significantly high compared with patients with non-BA.

In cases with positive screening tests or clinical jaundice with acholic stools, further investigation is needed to confirm the diagnosis of BA. These investigations are as follows: Abdominal ultrasonography serves as the cornerstone in the initial diagnostic approach for identifying the potential causes of obstructive cholestasis in neonates. This modality not only aids in the detection of alternate etiologies. In infants with BA, the gallbladder may appear small, measuring < 15-19 mm in the fasting state[59]. To optimize the accuracy of ultrasonography, the child must have fasted for 3-4 h before the procedure. Non-visualization of the gallbladder is a highly specific finding indicative of BA, although it does not confirm the diagnosis[60]. Additional gallbladder abnormalities associated with BA include the “ghost triad” or “pseudogallbladder”. This condition is characterized by a small gallbladder (< 19 mm) with an indistinct wall and irregular contour. Other findings included the triangular cord sign, absence of the

CBD, presence of microcysts or macrocysts near the porta hepatis, increased hepatic artery diameter (> 1.5 mm), peripheral arterialization, and polysplenia[60]. The triangular cord sign refers to a fibrous remnant of the obliterated biliary duct, which is observed adjacent to the anterior right portal vein wall. It is characterized by echogenic thickening of > 3-4 mm near the bifurcation of the main portal vein. In addition, the presence of cysts near the porta hepatis, in the absence of normal CBD, is a specific indicator of BA. Polysplenia has high specificity (100%) but low sensitivity (10%) for BA[59]. It is often associated with other signs of syndromic BA, such as preduodenal portal vein, absence of the inferior vena cava, absence of errant hepatic artery, and abdominal heterotaxy[61] (Table 2 and Figure 3).

Acoustic radiation force impulse can be a valuable tool for assessing liver stiffness or fibrosis, indirectly aiding in the diagnosis of BA. Various elastography techniques, including Virtual Touch Quantification (VTQ) and Virtual Touch IQ[66], transient elastography (TE)[67], and super shear wave elastography, have been explored for BA diagnosis. VTQ shows a sensitivity of 76.9%-90.9% and a specificity of 68.4%-78.6%[66,68,69]. However, the limited number of cases in studies raises questions about the reliability of this technique. TE measures liver stiffness, aiding in BA diagnosis. For infants aged < 90 d, a 7.7 kPa cutoff yields 80% sensitivity and 97% specificity, whereas for those aged 91-180 d, an 8.8 kPa cutoff provides 100% sensitivity and specificity[67].

Hepatobiliary scintigraphy (HBS) evaluates the anatomy and function of the biliary system, particularly the liver's capacity to excrete bile. A key indicator in these scans is the absence of radiotracer excretion into the small bowel within 24 h. HBS involves a protocol with phenobarbital (5 mg/kg/d in two divided doses) and ursodeoxycholic acid (UDCA, 10-20 mg/kg/d in two divided doses) for 5 d, which might increase the specificity of this investigation[70-72]. Although this finding strongly suggests the possibility of BA, it does not provide a definitive diagnosis. A meta-analysis revealed that HBS had a pooled sensitivity of 98.7% (range 98.1%-99.2%) and a specificity of 70.4% (range, 68.5%-72.2%) of a nondraining HBS for excluding BA[73]. NASPHAN and ESPGHAN concluded that their limited specificity precludes the use of BS scan as a

standalone test in making a definite BA diagnosis[74]. Other conditions characterized by impaired hepatocellular function and biliary excretion, such as neonatal hepatitis, can also result in the nonexcretion of the radiotracer into the small bowel[61,75].

Liver biopsy remains a pivotal component of BA diagnosis. However, the limitation of liver biopsy lies in the availability of skilled pathologists and the time required for the results. A meta-analysis of 22 articles revealed that preoperative liver biopsy exhibited an overall accuracy of 91.7%, sensitivity of 91.2%, and specificity of 93% (n = 1231)[76]. The PPV was 91.2%, and the NPV was 91.6% (n = 1106). In patients aged 60 d at presentation to diagnosis, the pooled sensitivity, specificity, PPV, NPV, and accuracy were 96.4%, 96.3%, 95.8%, 96.3%, and 94.9%, respectively. In the early BA stages, the liver maintains its basic structure, displaying features such as bile duct proliferation, bile stasis, and edema/fibrosis around the portal area. Bile plugs in portal ducts are specific but are present in only 40% of cases[4]. Older infants may exhibit extensive portal fibrosis. Approximately 25%-40% of infants exhibit inflammatory infiltration and giant cell transformation similar to neonatal hepatitis. This differs from idiopathic intrahepatic cholestasis, in which the bile duct remains largely unaffected. Edema in the portal area is more common in patients with BA. In very young infants, initial biopsies may be inconclusive; a repeat biopsy after 7-14 d may offer more clarity (Figure 4).

Intraoperative cholangiography

This invasive procedure is considered the gold standard for BA diagnosis. A contrast dye is injected into the gallbladder while the flow of the dye is monitored. If no contrast flows into the extrahepatic biliary ducts, BA is diagnosed, and a KPE is performed at that time.

Treatment surgical portoenterostomy

The primary treatment for BA is KPE. Despite attempts to enhance surgical techniques, the success rate of KPE remains suboptimal, with approximately 60% of patients with BA remaining transplant-free a decade postsurgery[77]. In addition, native liver

survivors are not considered cured because over half of them will experience complications of chronic liver diseases[78]. A long-term study in Japan in the 1970s, involving KPE, showed a 20-year NLS of 44%, but with notable morbidity, including recurrent cholangitis (37%) and gastrointestinal bleeding (17%)[79]. After KPE, medical management focuses on preventing and treating complications such as cholangitis and optimizing nutrition along with fat-soluble vitamin supplementation.

Medical treatment following hepatoportoenterostomy

The postoperative management of infants with BA has three main goals: Prevention of cholangitis.

Antibiotics: Common causative organisms include *Klebsiella spp.*, *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa*, and others. The infection likely ascends through the Roux loop into the intrahepatic duct system. The choice of drug, duration, and clinical benefit remain debatable. This involves administering broad-spectrum antibiotics perioperatively and for a few days after surgery. This is followed by oral prophylaxis with antibiotics such as trimethoprim–sulfamethoxazole or other antibiotics including cefalexin, amoxicillin-clavulanic acid, third-generation cephalosporin, or neomycin for 3-12 months with a cholangitis rate of 20%-78%[80].

Probiotics: The use of probiotics, such as Lactobacillus Casei Rhamnosus, is theorized to alter the microbiome toward a less harmful composition. However, reports on its effectiveness are limited. Lien *et al*[81] conducted a 6-month randomized study comparing oral neomycin and Lactobacillus Casei Rhamnosus. Although the study had statistical limitations because of its small sample size (n = 10), both groups showed a similar low prevalence of cholangitis (approximately 20%), which was notably better than a larger control group (approximately 80%). Stool cultures revealed a decrease in *E. coli* levels and an increase in Lactobacilli.

Stimulation of choleresis

UDCA: UDCA is a hydrophilic bile acid used to improve choleresis. Although studies have shown that it can lead to benefits such as weight gain and improved liver enzymes, its effect on long-term survival or the need for LT is less clear. In early trials from Japan[82], UDCA (15 mg/kg/d) with taurine supplements in 16 patients who underwent KPE showed promising results in lowering serum bile acid levels, even in patients with jaundice. A French study of patients with stable status post-KPE on UDCA (25 mg/kg/d) for at least a year found improvements in liver biochemistry but less pronounced effects on the clinical status[83]. The discontinuation and reintroduction of UDCA revealed its positive effect. However, a large retrospective study in Egypt[84] suggested that UDCA did not lead to better outcomes; however, the overall poor results may have influenced this observation. The combination of UDCA and steroids showed significant benefit in a meta-analysis[85].

Steroids: Steroids have been theorized to potentially improve biliary inflammation and enhance choleretic activity; however, their actual benefit in BA remains uncertain[86]. Some studies revealed that oral administration of prednisolone plays a role in improving jaundice shortly after surgery, particularly in infants aged 70 d. This improvement did not lead to a significant reduction in the need for LT[87,88]. The effectiveness of steroids was extensively evaluated in the multicenter, double-blind Steroid in Biliary Atresia Randomized Trial[89]. In this trial, infants received a 13-wk course of either high-dose steroids or a placebo within 72 h after KPE. The results showed no significant difference in TB levels at 6 months after KPE or in the 2-year survival rate with the native liver for those who received steroids. Moreover, the steroid group experienced growth impairment and a shorter time to the first serious adverse event. Although the authors could not rule out a slight clinical benefit, their findings did not support the routine use of high-dose steroids following KPE.

Provision of nutritional support: Patients with BA require increased caloric intake, approximately 130%-150% of the recommended allowance for their weight[90]. In cases of cholestasis, specific vitamin supplements are crucial to prevent deficiencies, such as vitamins A (5000-25000 IU/d), D (1200-4000 IU/d), E (25 IU/kg/d), and K (2.5-10 mg). Dosage should be adjusted based on blood levels and prothrombin time/international normalized ratio[4,90].

Other novel adjunctive therapies

Intravenous immunoglobulin: Intravenous immunoglobulin (IVIG) has demonstrated clinical benefits in various inflammatory and autoimmune diseases. It interferes with phagocytosis by innate immune cells, neutralizes autoantibodies, and modulates the adaptive immune response. In murine BA studies, high-dose IVIG administration resulted in decreased bilirubin levels, reduced bile duct inflammation and obstruction, and lowered cytokine levels associated with CD4+ Th1-mediated inflammation[91]. However, the overall survival did not show significant differences. By contrast, a prospective multicenter open-label human trial found no improvement in bilirubin levels 90 d after KPE or in 1-year survival with native liver in the IVIG group compared with the placebo group[92].

Rituximab: Recent studies have explored immune cell subset-specific therapies for BA. A small-sample study investigating B-cell-depleting agents showed that a single dose of rituximab was safe and well-tolerated; however, long-term clinical outcomes were not reported[93].

Granulocyte-colony stimulating factors: Another avenue involves hematopoietic stem cell recruitment through granulocyte-colony stimulating factors (GCSFs), which has shown promise in liver diseases. An ongoing clinical trial using GCSFs in patients with BA has demonstrated safety and potential improvement in early biliary drainage and

cholangitis frequency[94]. Additional treatment for BA mitigates ongoing hepatic injury caused by oxidative damage and bile acid toxicity.

N-acetylcysteine: N-acetylcysteine (NAC), an antioxidant, has been effective in improving hepatic injury and fibrosis and increasing survival in murine BA[95]. Currently, a single-center, open-label, phase 2 trial is investigating whether NAC administered after KPE can enhance bile flow in humans[96].

Ileal apical sodium-dependent bile acid transporter inhibitor: Clinical trials of novel agents that inhibit the ileal apical sodium-dependent bile acid transporter (ASBT), such as maralixibat and odevixibat, in BA are ongoing[97].

Farnesoid x receptor agonists: Farnesoid x receptor (FXR) agonists, which regulate metabolic homeostasis and inhibit bile acid synthesis, are potential therapeutic options for pediatric cholestatic liver diseases[98].

Prognosis and outcomes: The prognosis after hepatoportoenterostomy depends on several factors: (1) Age at operation is crucial for KPE. Bile flow can be restored in > 80% of infants operated upon within 60 d after birth. However, success drops to 20% for those aged > 90 d; (2) The size of the visualized ducts in the tissue from the porta hepatis. Ductal patency > 150 μm usually leads to successful postoperative bile flow. This is not universally accepted[80]; (3) The degree of proliferation of the periductular glands and the role of the hilar biliary plexus as a drainage route also affect prognosis[81]; (4) The experience and technique of the surgeon play a significant role; and (5) Others: Bacterial cholangitis that potentially leads to re-obstruction[4]. Approximately 20% of patients with BA may have intrahepatic biliary cysts, sometimes preceded by episodes of cholangitis[81]. Intrahepatic portal vein thrombosis can compound existing resistance because of progressive parenchyma fibrosis, often a consequence of ongoing inflammation or recurrent cholangitis. The hepatic artery

resistance index *via* Doppler ultrasound is predictive of rapid deterioration and mortality in children with BA[82].

Even with successful bile drainage, progressive biliary cirrhosis and liver failure can develop because of factors that have been previously described. When hepatoportoenterostomy fails, leading to worsening liver function, jaundice, failure to thrive, and complications, including bleeding and ascites, LT become necessary. The risk of death or the need for LT is approximately 50% within 6 years following the initial episode of esophageal variceal hemorrhage[99]. The prognosis depends on the initial bilirubin level; lower levels have a better survival rate. Among patients with serum bilirubin levels < 4 mg/dL during the first episode of variceal bleeding, > 80% experienced survival without needing LT for up to 4 years. When compared with an age-matched child without variceal bleeding, a patient with BA and bilirubin levels > 10 mg/dL faces a 12-fold higher risk of death or requires LT[99]. Moreover, hepatopulmonary syndrome can occur. It is reversible with LT but causes a higher postoperative risk. Portopulmonary hypertension, a severe lung condition linked to liver disease, is potentially fatal if left untreated. It requires careful evaluation, often with echocardiography.

Although the success rate of portoenterostomy in BA cannot be predicted, it remains the most prudent initial approach. A previous study followed the long-term outcomes of children who underwent portoenterostomy[100]. Approximately 75% had substantial hepatosplenomegaly. Only 9% of the children had normal liver enzyme levels and were free from portal hypertension. In a systematic review[101], 88% (n = 184) were alive without LT but with complications (60.5%) including cholangitis (100%), portal hypertension (80%), variceal bleeding (45%), and hepatocellular carcinoma (1.3%).

Approximately half of the patients with BA require LT by the age of 2, and most undergo LT in early adulthood. The global incidence of this condition varied widely. The 10-year survival rates ranged from 66.7% to 89%. The NLS rate was 20.3%-75.8% within 1-3 years and 24%-52.8% at 10 years. Beginning KPE at a younger age is linked to better NLS outcomes[82]. There is a growing awareness of the necessity to enhance

outcomes for patients who reach adulthood with their native livers. Recently developed prognosis models can help identify those at a higher risk of poor outcomes. Moreover, patients with BA are susceptible to neurodevelopmental challenges and a reduced quality of life. Studies have demonstrated varying degrees of motor and/or language skill impairment[83].

LT

BA is the leading indication of LT in children, accounting for approximately 50%-70% of pediatric LT cases[102,103]. Today, advancements in preoperative management, surgical techniques, and postoperative care have resulted in high survival rates for children undergoing liver replacement by nearly 90%-95%[102,104]. However, the scarcity of suitable donor organs remains a significant challenge. Reduced-size LT has proven successful in improving patient survival and reducing waiting-list mortality rates[105]. Overall, while LT has a high success rate in children, ongoing challenges are noted. These include improving preoperative management of conditions such as malnutrition, enhancing immunosuppression methods to prevent graft rejection and complications, and developing protocols to avoid growth suppression.

In an upcoming study on LT as primary therapy for BA, Chardot *et al*[106] showed a 10-year survival rate of 68%. Factors affecting survival included KPE, age at operation, bile duct anatomy, and center expertise. Lemoine *et al*[107] retrospectively compared patients with BA who underwent primary LT with those who had a prior KPE. The findings indicate that patient and graft survival after primary LT is comparable to that after unsuccessful KPE; however, primary LT eliminates the need for prior interventions. Except for waiting-list mortality, no significant differences were found in pre- or peri-transplant complications between the groups.

Bile duct hypoplasia

Bile duct paucity is characterized by a specific histopathological criterion: A bile duct to hepatic artery ratio of < 0.5, observed in at least 10 portal tracts in a liver biopsy. The

more prevalent and well-studied syndromic form is AGS, also known as arteriohepatic dysplasia. The nonsyndromic form, not linked to AGS, is rare and lacks comprehensive characterization. The development of bile duct paucity can be attributed to either faulty formation of intrahepatic bile ducts in the prenatal or postnatal period or active destruction/atrophy of the already formed ducts[108]. Factors such as in utero toxins, infections, and metabolic abnormalities can lead to toxic effects on bile duct cells, progressing from an inflammatory cholangiopathy to bile duct paucity shortly after birth. Prompt and accurate diagnosis is vital because of the clinical similarities between bile duct paucity and classical BA. This guides appropriate management, with surgical intervention for BA and more conservative approaches for bile duct paucity. In the case of bile duct paucity, International Olympic Committee shows bile duct hypoplasia that can differentiate from BA (Figure 5A). In addition, nonsyndromic bile duct paucity has been linked as a secondary outcome to metabolic disorders, genetic disorders, infections, immune disturbance, and drug-induced vanishing bile duct syndrome (Table 3).

Syndromic bile duct paucity or AGS

AGS is an autosomal dominant genetic disorder that affects multiple body systems. AGS was first identified by Daniel Alagille in 1969[111]. AGS is primarily caused by JAGGED1 (JAG1) mutation, which is responsible for producing the Jagged protein in the Notch signaling pathway[112]. Over 90% of patients have a detectable mutation in JAG1. However, the rest have NOTCH2 mutations[113]. Even with the same genetic mutations, individuals within a family show different AGS characteristics.

Criteria for diagnosis and clinical manifestations

The traditional diagnosis criteria for AGS involved liver histology showing reduced bile ducts and three of the five major clinical features: Cholestasis, eye abnormalities, distinct facial features, cardiac defects, and skeletal abnormalities. Recent findings have expanded the criteria, and liver biopsy is no longer mandatory; cholestasis alone is

sufficient for diagnosis (Table 4). Moreover, ≥ 4 major criteria are required for the diagnosis of AGS. In the presence of a familial history of AGS, the presence of JAG1 mutation is diagnostic of AGS even if the above criteria are nonexistent. If either a genetic mutation or familial history is positive, at least one major criterion is needed to make the diagnosis.

A molecular diagnosis is confirmed in approximately 96% of individuals. The majority of JAG1 and NOTCH2 mutations can be detected by sequencing all exons and adjacent intronic regions for splice site mutations in each gene. Because JAG1 mutations are more common, this gene is sequenced first. This is followed by analysis for deletions or duplications using methods such as multiplex ligation-dependent probe amplification, chromosomal microarray, or fluorescence *in situ* hybridization. In cases where no JAG1 mutation is found, sequencing of NOTCH2 uncovers an additional 2%-3% mutation in AGS[117]. For the remaining 2%-4% of patients with clinically diagnosed AGS without an identified causative mutation, employing various next-generation sequencing techniques could reveal the molecular origin in this subgroup[111].

TREATMENT

Nutritional management

Dietary recommendations have been established for children with cholestasis (Table 5). Moreover, chronic cholestasis leads to osteopenia and fractures, particularly in the long bones. This is worsened by genetic abnormalities in JAG1 and NOTCH2, which are crucial for bone formation and regulation. Frequent fractures often signal the need for LT in patients with AGS. In cases of chronic cholestasis, initiating vitamin D supplementation and providing calcium at a dosage of 50-100 mg/kg/d and phosphorus at 25-50 mg/kg/d are essential[114].

Symptomatic treatment

Pruritus: Medical intervention for pruritus typically combines various approaches, including choleretics, antihistamines, rifampin, and opiate antagonists such as

naltrexone[110,119]. Recent investigations have explored sertraline as an alternative treatment for pruritus in AGS and related cholestatic disorders[119]. Recently, ASBT inhibitors have been studied for pruritus treatment in AGS[120]. Maralixibat, an ASBT inhibitor, showed promising results in reducing pruritus in children with AGS[121]. Similarly, odevixibat, another ASBT inhibitor, improved pruritus and reduced serum bile acids[122] (Table 6).

In severe cases, surgical biliary diversion may be considered. Partial external biliary diversion (PEBD) is a frequently performed procedure in which the gallbladder is externally drained through a jejunal conduit. Wang *et al*[124] found positive outcomes in 20 patients with AGS who underwent PEBD, including improvements in total serum cholesterol, pruritus severity, and xanthoma. Ileal exclusion and internal biliary diversion are less commonly performed procedures.

Hypercholesterolemia: Xanthoma is a sign of hypercholesterolemia in AGS (Figure 5C). A previous study reported that patients with AGS exhibit varying lipoprotein patterns based on the extent of hyperbilirubinemia[125]. Patients with AGS with mild hyperbilirubinemia (TB < 5.8 mg/dL) have high levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), as well as high levels of serum apoprotein A-I and apoprotein A-II. Conversely, severe hyperbilirubinemia (TB > 5.8 mg/dL) is associated with dyslipidemia, characterized by reduced levels of LDL-C and HDL-C, accompanied by diminished apoprotein A-I and apoprotein A-II levels[125]. Hypercholesterolemia in AGS is also linked to the presence of lipoprotein X, a type of low-density lipid composed of phospholipids, albumin, and free cholesterol. Lipoprotein X is not considered atherogenic, which means that it does not contribute to an increased risk of cardiovascular disease[126]. Therefore, it does not necessitate dietary adjustments or medical intervention. However, the debate continues regarding whether hypercholesterolemia in AGS leads to atherosclerosis. Some published reports have documented instances of atheromatous vascular disease in patients with AGS[127,128]. Nakajima *et al*[129] documented successful combination therapy

using atorvastatin and fenofibrate to reduce refractory dyslipidemia in patients with AGS. However, the study did not address other prognostic factors, particularly the NLS rate.

LT

LT is mainly recommended for patients with AGS and advanced liver disease. Other indications include the development of hepatocellular carcinoma or uncontrollable itching or frequent fractures. In evaluating suitability for LT, the involvement of multiple systems, including the heart, kidneys, and blood vessels, must be considered. Patients should undergo brain magnetic resonance imaging (MRI)/magnetic resonance angiography, abdominal computed tomography (CT), and echocardiography as part of the assessment for LT. Regarding living-related LT, donors with JAG1 or NOTCH2 mutations must be avoided[130].

Advanced therapy

Experimental research suggests that AGS offers a unique opportunity for developing therapeutic approaches targeting Notch pathway signaling to enhance cholangiocyte differentiation[131,132]. Unlike structural heart defects, intrahepatic bile duct development continues postnatally. Studies have indicated the potential to target this process to improve the manifestations of cholestatic liver disease. Research is underway to develop personalized therapeutic approaches that could alleviate the clinical manifestations of AGS. Various *in vivo* and *in vitro* models of AGS have been developed to gain a better understanding of the disease. Mouse models that focus on perturbations in the Notch signaling pathway have been instrumental in studying AGS[132]. Cell-based models, including bipotent liver progenitor cells and organoid cultures, provide physiologically relevant systems for studying the hepatic features of AGS. Recent advancements in the generation of human hepatic organoids from induced pluripotent stem cells show promise in mimicking liver development and regeneration. These

organoids displayed deficiencies in forming duct structures compared with controls[133-135].

Prognosis and outcomes

Liver disease in AGS can range from mild to severe cholestasis. This leads to malnutrition, deficiencies in fat-soluble vitamins, itching, and xanthomas. Growth failure is common in AGS and can be sufficient to warrant LT. Failure to thrive results from various factors, including genetics, cholestasis, malnutrition, vitamin deficiencies, and associated renal or cardiac problems[110]. These studies also reported abnormal bleeding in patients with AGS. Intracranial bleeding, including subarachnoid, subdural, and epidural hemorrhage, is the most common type, occurring in 11%-14% of cases[136,137]. Mortality over a 10-40-year follow-up ranged from 11% to 35%. The median age at death varied from 2.3 to 4 years[138,139]. Some studies have assessed the health-related quality of life in patients with AGS, and pruritus affected a substantial portion, ranging from 59% to 82% of patients[123,140]. Itching was associated with other symptoms such as skin damage, sleep disturbances, and mood disorders.

Infants with AGS are occasionally misdiagnosed with BA and subsequently undergo KPE. A recent study of 394 patients with AGS found that those who underwent KPE had significantly higher incidences of LT and mortality than those who did not undergo KPE[141]. However, studies have indicated that approximately 20%-30% of patients with AGS may eventually require LT[136]. Recent reports suggest that this number may be even higher, especially for those who develop cholestatic liver disease early in life. In addition, individuals with AGS are at risk of developing hepatocellular carcinoma[142].

Studies have identified specific markers that can predict later outcomes. For instance, high levels of TB (> 6.5 mg/dL), conjugated bilirubin (> 4.5 mg/dL), and cholesterol (> 520 mg/dL) in children aged < 5 years can predict severe liver disease later in life[143]. This cohort study is constrained by its small sample size and a method for aggregating laboratory data from ages 0-5 years rather than analyzing them annually. Consequently, the predictor may not be widely validated. The type of JAG1 mutation does not appear

to affect the outcomes. A larger study involving 144 patients with AGS further supported these findings, indicating that the presence of fibrosis on liver biopsy before the age of 5 years, xanthomas, and TB > 3.8 mg/dL between the ages of 1 and 2 years were predictors of severe long-term liver outcomes[144]. A recent study followed 293 patients with AGS and found that markers of cholestasis tended to peak in infancy and normalize over time[145]. However, complications related to portal hypertension become more common as patients reach the age of 20 years. By this age, 40% of the cohort met the criteria for clinically evident portal hypertension[146]. Overall, the transplant-free survival rate at the age of 18.5 years was 24%. This suggests that while cholestasis is most pronounced in the early years, portal hypertension and associated complications often develop later, sometimes necessitating LT during childhood[147]. By contrast, other cholestatic liver diseases, such as BA, tend to show signs of portal hypertension earlier. For instance, in one study, splenomegaly was reported in 56% of children with BA by the age of 10 years[147].

A meta-analysis study focused on LT in AGS. They reported that 15%-47% of the patients underwent LT, typically between the ages of 4 and 6.5 years[148]. Common indications for LT include severe pruritus, xanthoma, bone fractures, and signs of advanced liver disease. A study revealed that 79% of patients who underwent LT survived, with an average follow-up of 4.2 (range, 0.7-12.3) years[136]. Children with AGS demonstrated lower survival rates than those with BA at the 1-year mark (87% *vs* 96%)[149]. Deaths after LT were primarily caused by complications, with most occurring within the first 30 d. The most frequent post-LT complications were vascular, biliary, and renal problems. Moreover, children with existing kidney problems were less likely to show improvement after LT[149].

Gallstones/inspissated bile syndrome

Pathogenesis: Generally, bile has five major components: Water, bilirubin, cholesterol, bile pigments, and phospholipids. Cholesterol is a precursor for the synthesis of bile acids. Within hepatocytes, cholesterol is converted into primary bile acids, namely,

cholic acid and chenodeoxycholic acid, in humans by a complex biochemical pathway involving several different hepatic enzymes. Stone formation occurs from the insoluble components of bile, which are cholesterol, bile pigments, and calcium salts. Nearly all gallstones are a mixture of compositions[150]. Gallstones, also known as cholelithiasis, are an unusual condition in neonates and children. The pathogenesis of stone formation is often multifactorial. Normal bile compositions require an equilibrium percentage of cholesterol, bile salt, and lecithin (phospholipid) in a triangular diagram (Figure 6). It usually comprises mechanisms that alter either bile composition or gallbladder motility. First, supersaturated bile with cholesterol affects crystal precipitation. The overexpression of ABCG5 and ABCG8 transporters promotes biliary sterol secretion and decreases the absorption of dietary cholesterol. Second, bile kinetics permits nucleation. Finally, gallbladder stasis allows the integration of cholesterol crystals into stones[150]. The different characteristics of cholesterol and pigmented gallstones in children are shown in Table 7.

In the neonatal period, principally premature and small-for-gestational-age neonates with sepsis, prolonged use of diuretics, narcotics, antibiotics, dehydration, or receiving total parenteral nutrition are at risk for gallstones or inspissated bile syndrome[150]. Some genetic factors are susceptible to gallstone formation. Despite the lack of existing specific genes, some possible genes include the human LITH genes lith1 (ABDB11) and lith2 (ABCC2). These gene loci lead to overexpression, which causes stone formation by promoting biliary sterol secretion and decreasing dietary cholesterol absorption[152]. Other genetic diseases of biliary transport can lead to infantile gallstones, including bile salt export pump deficiency, multidrug resistance three deficiency[150], and pigmented stone formation disorder in cystic fibrosis. The rising incidence starts with greater ultrasonographic surveillance. In children and adolescents, those with genetic causes include hemolytic anemia, which often increases bilirubin production, such as thalassemia, hereditary spherocytosis, sickle cell disease, or erythrocyte enzyme defects (*e.g.*, pyruvate kinase deficiency; Figure 7)[152]. Additional risk factors include dyslipidemia, hypercalcemia, a history of ileal resection, or a family history of

gallstones. Ceftriaxone is an antibiotic that is related to biliary stones with dose dependence (Figure 8). It is involved in many proposed mechanisms, such as the high calcium-binding affinity of ceftriaxone, abnormal drug excretion, and impairment of bile flow (Figure 9). Children may present with abdominal pain, jaundice, nausea, and vomiting or may be asymptomatic. This type of cholelithiasis may resolve over a varying period, from days to months after the termination of therapy[153]. Gallstones are classified as cholesterol stones (70% of gallstones) and pigmented (black or brown) stones. There are different characteristics, such as color, composition, risk factors, age, size, number, radiopaque, and recurrence, as shown in Table 7.

Clinical signs and symptoms

The presenting signs and symptoms vary among all age groups. Infants usually have jaundice but sometimes have nonspecific presentations. In older children, classic symptoms include right upper quadrant pain and vomiting. Fever is an unusual finding at any age, and it can present when complications occur, such as cholecystitis or cholangitis. A single large gallstone or multiple gallstones can pass and cause biliary tract obstruction, including choledocholithiasis when the CBD is blocked, pancreatitis when the pancreatic duct is obstructed, or gallbladder perforation. However, gallstones can often be found incidentally on abdominal ultrasound with no symptoms.

Investigation

Transabdominal ultrasound is frequently used to detect gallbladder stones with a sensitivity of up to 96%, and the sensitivity to detect CBD stones drops to ≤ 50% because bowel gas patterns usually obscure clarity. The indirect sign includes CBD dilatation, although this is contentious as the size of CBD varies between 5 and 11 mm with an increase in size, which is related to older age and/or postcholecystectomy[154].

Treatment

Medical treatment: No definite management guidelines have been established for children with asymptomatic gallstones and normal liver function tests. Medical treatments, such as UDCAs and cholesterol-lowering agents, may prevent the formation of new stones but do not help in the dissolution of gallstones.

FXR agonists such as obeticholic acid are new drugs that activate the FXR pathway by inducing fibroblast growth factor 19 transcription and CYP7A1 inhibition, which is the first and rate-limiting enzyme in bile acid synthesis. This drug can decrease chloride secretion to calcium and cAMP-dependent agonists in the intestinal epithelium, which was previously proposed to treat cholesterol gallstone disease and cholestasis[155].

Surgical treatment: Two surgical management approaches are available: Open and laparoscopic approaches (Figure 10). In asymptomatic children, particularly those at high risk of stone formation due to hemolytic anemia, elective cholecystectomy is recommended because the incidence of spontaneous resolution is very low during childhood. However, symptomatic children at high risk may prefer the laparoscopic approach of cholecystectomy. Laparoscopic techniques usually require a shorter hospital stay and cause fewer complications such as bile duct injury, particularly in younger children[152].

Endoscopic retrograde cholangiography (ERCP) is performed in patients with stones in the CBD. This can be performed even if the patient has an unstable status. Even in young children, ERCP may be too difficult to perform or not available. Intraoperative cholangiography can identify stones in the CBD. Thus, it may be necessary to perform cholecystectomy at the same time to clear the common bile stones[152].

Nowadays, percutaneous cholecystostomy by interventional radiologists is a standard procedure designed for bile drainage. It can be accessed *via* a percutaneous transhepatic or transcholecystic approach and removes multiple stones in both intra- and extrahepatic bile ducts that obstruct the distal biliary tract. This procedure successfully manages acute calculous cholecystitis, acalculous cholecystitis, and biliary

stricture in tumors. Percutaneous cholecystostomy is a vital lifesaving procedure for patients with critical illness[156] (Figure 11).

CDCs

CDCs are congenital malformations of the biliary tract that dilate the intra- and/or extrabiliary tree. These cysts are often associated with an abnormally long common channel between the biliary and pancreatic ducts, *i.e.*, anomalous pancreaticobiliary duct union (APBDU)[150,157].

Clinical signs and symptoms

Typically, CDCs are found symptomatic during childhood, approximately 20% are diagnosed in adulthood, and 15% are diagnosed antenatally[158]. However, they are often an incidental finding[150,159]. Infants classically present more likely with cholestasis, whereas older children and adults present with abdominal pain or pancreatitis. Some patients may have a right upper quadrant abdominal mass[150,160]. Clinical presentation varies and most often consists of nonspecific abdominal pain[159]. The category of CDCs was based on operative records and radiological imaging findings. In 1977, Todani *et al* modified the original Alonso-Lej classification to include five types of CDCs, as shown in Figure 12 and Table 8. It is categorized by the type of dilatation (intrahepatic and/or extrahepatic bile ducts), cystic or fusiform, and locations in the biliary tree. Types I (85%) and IV (10%) are the most common and most probably associated with malignancy. Associated complications occur following stasis of bile or infection. Cyclothiasis and cholangitis are the most common. Other complications such as hepatolithiasis, portal hypertension, spontaneous perforation, acute or chronic pancreatitis, and complications are related to incomplete cyst excision[157]. Long-term sequelae involve bile duct stenosis, anastomotic stricture, and hepatobiliary malignancies[158].

Differential diagnoses of CDCs include biliary stones, pancreatic pseudocysts, polycystic liver disease (Caroli's disease), primary sclerosing cholangitis, biliary

hamartoma, bile duct tumor, and CBA, which suggest CDCs. CBA must be differentiated from CDCs because of the permanently aggressive long-term sequelae of late treatment in CDCs[162].

Investigation

Transabdominal ultrasonography is the most commonly used modality for diagnosis because it does not require radiation and is valid and efficient for pediatric patients. It should be initially performed for evaluation in patients suspected of having CDCs. Antenatal ultrasonography could reveal incidental findings of CDCs; however, its accuracy is unclear[161] (Figure 13). Other imaging, such as CT, MRI, or MRCP, may be used in some conditions such as when ultrasonography is unable to determine the cause of a dilated CBD in one-third of patients or certainly identify anomalous pancreaticobiliary duct union. Endoscopic ultrasonography is safe and accurate under these circumstances, particularly in its ability to detect a long common channel and choledochoceles. ERCP stands for the gold standard of this diagnosis. The radiographic appearance of liver cysts could mimic Caroli's disease or CDC type V, in which the cysts involved in polycystic liver disease are not connected to the biliary tract (Figure 14). In addition, intrahepatic biliary dilatation is indicated for additional imaging beneficial to discriminate type I CDCs from type IVa[162] (Figure 15).

Treatment

Complete surgical excision is recommended when the diagnosis is made, even if the timing is controversial according to the prenatal diagnosis, age at presentation, and coexisting signs and symptoms. In the postnatal period, definitive surgery is performed at the age of 3-6 months because of the caution in general anesthesia and surgery in neonates. The appropriate timing of surgical intervention depends on the clinical presentation. In cases where cholangitis or pancreatitis is the presenting symptom, intervention often must be held until the inflammation wanes. The definite intention is complete surgical excision of the cyst mucosa, with Roux-en-Y choledochojejunostomy

proximal to the most distal lesion. It results in the bile duct mucosa directly connecting to the bowel mucosa anastomosis, with the lowest risk of stenosis or stricture. Other historical procedures include aspiration and external drainage, internal decompression, and drainage to the duodenum, namely, cyst duodenostomy, or direct anastomosis to the jejunal Roux-en-Y loop[163]. However, all techniques spared the abnormal mucosa of the cyst wall. The presently recommended treatment includes the elimination of the entire cyst mucosa by complete excision of the extrahepatic cyst and the extrahepatic biliary tree with the creation of a retrocolic, isoperistaltic jejunal Roux-en-Y loop of 35-45 cm. Inadequate drainage leads to stasis and persistent cyst inflammation, resulting in stricture formation, biliary stones, and an increased risk of malignant progression inside the cyst wall[161].

The extent of any intrahepatic cystic disease is important to define at the time of CDC excision. Optimal attempts are intraoperative cholangiography or preoperative percutaneous transhepatic or ERCP. Unless the cystic disease does not continue with the primary bile duct cyst and has strictures leading to stasis, reconstruction of the hepatic hilum is an appropriate procedure. In Caroli's disease, which is an intrahepatic cystic disease, interposed areas of stenosis are present; thus, this decompressive method is not suitable. Segmental multifocal cystic disease isolated to a single hepatic lobe can be successfully cured by cyst excision and hepatic lobectomy. In a diffuse intrahepatic disease that involves all hepatic lobes, if complete and successful decompressive drainage is not applicable, LT may be essential[161,163].

Prognosis and outcome

The incidence of complications, including cholangitis, bile leaks, and anastomotic stricture, is approximately 2%-3% in both Roux-en-Y and hepaticoduodenostomy. Pancreatitis is rare; however, it is secondary to stenosis or stones in the proximal pancreatic duct or sphincter[161].

Although CDCs are benign, they may increase the risk of cancer in 10%-20% of all cases[162] and remain in 3% of cases after surgical excision in the general population[164].

Biliary cancer is uncommon in children with CDCs; however, the likelihood of its development increases as the patient gets older at the time of diagnosis. Whether the elevation of malignancy risk is associated with incomplete excision or innate biliary cancer susceptibility is indefinite. CDC type I or IV has a higher risk of developing biliary cancer after resection. If diagnosed with a CDC, prompt operative resection is necessary. Long-term surveillance is recommended to monitor the development of biliary cancer. Early detection and treatment can greatly improve prognosis[164].

CONCLUSION

Overall, bile duct diseases in children typically present with jaundice, abdominal pain, or fever. Although these conditions can occur at any age from birth through adolescence, they are most commonly seen in the first year of life. CBD diseases in children include BA, biliary hypoplasia, inspissated bile syndrome, and CDCs. Cholestatic jaundice can lead to several complications, including malnutrition, liver damage, and liver failure. Early diagnosis and treatment are essential to prevent these complications. Some cases can be managed conservatively, for example, in cases of asymptomatic gallstones or AGS. Many of these conditions require surgical intervention to resolve bile duct obstruction. Some of the most common surgical treatments include KPE for BA, excision with Roux-en-Y choledochojejunostomy or decompression drainage for CDCs, and ERCP and cholecystectomy for gallstones.

However, some, such as those with a genetic predisposition to BA or metabolic diseases, might require further research for effective applicability in patients. Advanced therapy experimental research has found that AGS presents a special opportunity for developing therapeutic approaches that focus on Notch pathway signaling to improve cholangiocyte differentiation. Lastly, LT is a viable option indicated in cases of decompensated liver diseases or some specific complications. The prognosis depends on the initial bilirubin levels; lower levels have a better survival rate in most cases with lower toxicity to the hepatocyte and decreased risk of malignancy.

Moreover, the use of basic to advanced imaging and investigations is important for early detection and decreases complications. Novel investigations and therapies for each disease were developed for a less invasive approach with a more favorable outcome and lower serious long-term complications.

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