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Biliary Atresia:

Recent Progress

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Abstract

Extrahepatic biliary atresia (EHBA), an inflammatory sclerosing cholangiopathy, is the leading indication for liver transplantation in children. The cause is still unknown, although possible infectious, genetic, and immunologic etiologies have received much recent focus. These theories are often dependent on each other for secondary or coexisting mechanisms. Concern for EHBA is raised by a cholestatic infant, but the differential diagnosis is large and the path to diagnosis remains varied. Current treatment is surgical with an overall survival rate of approximately 90%. The goals of this article are to review the important clinical aspects of EHBA and to highlight some of the more recent scientific and clinical developments contributing to our understanding of this condition.

Keywords

biliary atresia; pediatrics; chronic liver disease; liver transplantation; portoenterostomy

Extrahepatic biliary atresia (EHBA) is an inflammatory, progressive, fibrosclerosing cholangiopathy of infancy, affecting both the extrahepatic and intrahepatic bile ducts to a variable extent^{1,2} that results in destruction and obstruction of the biliary tract.^{3,4} Without medical and surgical intervention, disease progression leads to hepatic fibrosis, cirrhosis with portal hypertension, liver failure, and death within 2 to 3 years. It classically presents in 1 in 8000 to 1 in 18,000 livebirths, during the neonatal period, with cholestatic jaundice, acholic stools, and hepatomegaly, in an otherwise apparently healthy infant.^{2,5–8}

Evidence to date supports a number of possible pathogenic mechanisms for EHBA but the exact pathogenesis remains unknown and is the focus of much current research. EHBA uncommonly recurs in families and is rarely concordant when it occurs in twins.^{9–11} A higher incidence is reported in 1 study of mothers of advanced age, multiple gestations, and

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premature and small for gestational age infants.¹² The literature reports conflicting results for seasonal variation in incidence of EHBA.

Optimal treatment strategies are also under investigation, but the primary therapy for EHBA remains surgical. If applied in the first 3 months of life, a hepatoportoenterostomy can successfully restore bile flow from the liver to the intestine in 40% to 80% of patients,^{13,14} with the highest success observed when performed before 60 days of age. When this initial surgery does not restore bile flow, liver transplantation can be life saving and EHBA is the most frequent indication for liver transplantation in children, representing more than 50% of cases in most series.^{6,15,16}

The goals of this article are to review the important clinical aspects of EHBA and to highlight some of the more recent scientific and clinical developments in our knowledge of this condition.

CHARACTERIZATION

Attempts to characterize the disease on the basis of differing phenotypes have led to the description of anatomical and clinical subtypes. On the basis of patency of the hepatic bile duct, 2 different anatomical subtypes are described: correctable and uncorrectable. The correctable subtype is characterized by a patent hepatic duct up to the porta hepatis without duodenal communication, and may allow for a direct extrahepatic biliary duct-intestinal anastomosis. This correctable subtype accounts for only 10% to 15% of the biliary atresia patients. No lumen is available for bile duct-intestine anastomosis in the noncorrectable type.^{17,18}

Two different subtypes on the basis of clinical characteristics have also been proposed: the fetal or syndromic form and the perinatal or acquired form.^{1,2,19-21} The fetal type is characterized by early cholestasis without a jaundice-free period after the physiologic jaundice should have subsided. Stereotypical coexisting congenital anomalies complicate this fetal type of biliary atresia, which has an estimated incidence of 10% to 25% of infants diagnosed with EHBA. Coincident congenital anomalies could include intestinal malrotation, asplenia or polysplenia, portal vein anomalies (preduodenal, absence, cavernous transformation), situs inversus, congenital heart disease, annular pancreas, Kartagener's syndrome, duodenal, esophageal or jejunal atresia, polycystic kidneys, and cleft palate. It has been suggested that these clinical associations may indicate a common pathogenesis.^{20,22,23} In contrast, the more common perinatal type of EHBA usually presents with cholestatic jaundice between 1 and 2 months of age and does not have coincident congenital anomalies.

ETIOLOGY AND PATHOGENESIS

The cause of biliary atresia is not known. Multiple theories as to the pathogenesis of EHBA differ in the proposed primary mechanism of injury, but they are often similar in their dependence on secondary or coexisting factors.

Immune-mediated Ductal Injury

The presence of lymphocytic infiltration of the portal tracts in liver biopsy specimens of infants with EHBA has suggested a primary inflammatory process leading to bile duct obstruction. The mechanism by which lymphocytes induce bile duct damage is still unclear,^{24,25} and research on potential triggers of this inflammatory response will be discussed later. Proinflammatory cytokines such as interleukin (IL)-2, IL-12, interferon (IFN)- γ and tumor necrosis factor (TNF)- α have repeatedly been shown to be prominent in livers with biliary atresia. Kupfer cells, CD4⁺ and CD8⁺ T cells, and natural killer cells have also been demonstrated.^{15,26-28} The predominance of T-cell infiltration and a type 1 response has been increasingly implicated in the pathogenesis of biliary atresia.²⁶⁻³⁰ Additional immunologic investigation has revealed that, when compared with controls, there are a significantly higher number of CD3⁺ and CD8⁺ lymphocytes and also CXCR3⁺ mononuclear cells in the portal tracts of children with EHBA.³⁰ Furthermore, the loci of CXCR3⁺ cell infiltration within the biliary specimen coincided with those of CD3⁺ and CD8⁺ lymphocyte infiltration. This finding suggests that most of the CXCR3⁺ cells were T lymphocytes rather than natural killer cells. These observations further indicate a T-helper type 1 inflammatory response.

Mack et al³¹ have attempted to further understand the CD4⁺ and CD8⁺ T-cell populations. They have proposed that the pathogenesis of EHBA involves a virus-induced, autoreactive T-cell-mediated injury of bile duct epithelia. It was found that there are oligoclonal expansions of both CD4⁺ and CD8⁺ T cells within the liver and extrahepatic bile duct tissues of patients with EHBA. The composition of the oligoclonally expanded T-cell populations suggests their accumulation in response to specific antigenic stimulation. The particular antigens responsible for this T-cell activation will form the basis of future study.

Recently, Mx proteins, which mediate an early innate immune response, were found to be upregulated in the bile ducts and endothelial cells of the hepatocytes in patients with biliary atresia compared with controls.³² Mx proteins are a very sensitive marker for type 1 IFN activity, which is known to mediate the early innate response to viral infections. Although this is suggestive of viral involvement, it remains unclear whether a virus is responsible for the development of EHBA or coincident in this infant population. It is also remarkable that all patients in this study were serologically negative for tested hepatotropic viruses.

Although an inflammatory component has been repeatedly demonstrated, the exact pathogenesis and trigger are unknown. The nature of the inflammatory response and what triggers it remain areas of active research.

Viral Agent as an Inflammatory Trigger

It has been suggested by many that the trigger for the inflammatory cascade may be a hepatotropic viral infection. The viral infection may lead to an initial bile duct epithelial injury that triggers a persistent immune-mediated sclerosing process and results in obstruction of extrahepatic bile ducts.^{28,33-35} There have been many hypotheses and studies to identify the etiologic virus. Potential candidates have included cytomegalovirus,^{36,37} human herpes virus,³⁶ human papillomavirus,³⁸ group C rotavirus,³⁹ and reovirus.⁴⁰ The

suggestive results have been largely underpowered and inconsistent, whereas other studies have disputed their role.^{41–44} Examples of the conflicting studies include those of reovirus and rotavirus, which are the most common infectious agents currently associated with EHBA.³ One study found reovirus RNA (ribonucleic acid) in hepatocytes and/or biliary tissue in 55% of the patients with EHBA using RT-PCR (reverse transcription-polymerase chain reaction),⁴⁰ suggesting a possible causal role whereas others refute the causal association.^{35, 42, 44, 45} Similarly, studies have also demonstrated the presence of rotavirus RNA in 50% of patients with EHBA,^{40, 46} but the frequency of this infection in this infant group has fueled doubt on the causal relationship with biliary injury.

Although the human evidence for rotavirus as the etiologic trigger of EHBA is mixed, the development of a rotavirus-induced animal model that simulates EHBA strengthens the theory. The infection of newborn mice in the first 24 hours of life with rhesus rotavirus leads to generalized jaundice, acholic stools, and bilirubinemia by the end of the first week of life. Progressive inflammation and obstruction of the extrahepatic bile duct is observed by 2 weeks of age, resembling human EHBA.^{46–49} These effects of rhesus rotavirus infection have been reliably replicated in various laboratories.^{46, 48, 50} Although this animal model indicates that EHBA could be the result of a viral infection, the evidence in human beings remains inconclusive.^{46, 48, 51} The similarity between the immune response seen in human EHBA and the rotavirus-simulated animal model, however, demonstrates the potential for use of the animal model as a powerful tool to hopefully further elucidate the pathogenesis of EHBA. In this animal model, the bile duct injury is associated with an initial CD4⁺ T_H1 cellular response that, by the release of IFN- γ , activated macrophages to produce TNF- α and nitric oxide.⁵² Interestingly, this response persisted despite documented viral clearance.

The main criticism of the hypothesis of a viral infection as the primary trigger for EHBA is the inability to document the presence of any virus in many patients with EHBA. It is possible, however, that early timing of the infection, and a short period of active infection prevents viral detection by the time of clinical presentation. For example, it is plausible that a perinatal infection with a virus that is tropic for the bile duct epithelia would cause initial bile duct epithelial injury. After viral clearance, persistent inflammation and injury to the bile duct epithelia results, with ultimate EHBA. This seems plausible given that in the murine model there is clearance of virus, 14 days after infection but continued injury to the biliary ductules.^{50, 52}

Predisposing Genetic Factors

It has been hypothesized that there could be a genetic component to the development of EHBA. α -1- antitrypsin (A1AT) deficiency is the most common genetic cause of liver disease.⁵³ The impact of A1AT heterozygosity as a modifier of other forms of pediatric liver disease, however, is only now being realized. Campbell et al⁵⁴ demonstrated that A1AT non-M alleles are more frequent in children with liver disease than in the general population. The frequency of A1AT heterozygosity was also significantly higher in the children with EHBA. In fact, in these patients the presence of a non-M allele was associated with a rapid progression of disease and earlier age at transplant listing, implicating A1AT heterozygosity as a potential contributor to disease severity. Screening for A1AT heterozygosity across the

entire disease population is currently being facilitated by the Biliary Atresia Research Consortium (BARC), a National Institute of Digestive Diseases and Kidney-sponsored clinical research network (<http://www.barcnetwork.org>).

Other potential genetic factors have been suggested. The transgenic “inv” mouse has a recessive deletion of the inversin gene and develops situs inversus and extrahepatic biliary obstruction.^{8,55} The inversin gene has tandem ankyrin-like repeat sequences expressed in the liver, kidney, and other tissues early in embryonic life. It is notable that extrahepatic biliary obstruction only occurs in the inv mouse and not in other mouse models of situs inversus. Also, mutations in the human Jagged 1 gene, which are responsible for the Alagille syndrome, have been associated with cases of EHBA. The Jagged 1 gene encodes a ligand in the Notch signaling pathway, which is critical to the determination of cell fate during development. Expression of the Jagged 1 protein in a hepatoma cell line altered production of the inflammatory cytokines TNF and IL-8.⁵⁶

Human leukocyte antigen (HLA) type has also been considered as a factor in genetic predisposition to ductular injury. A significantly high frequency of HLA B12 alleles has been repeatedly found in patients with EHBA, specifically haplotypes A9-B5, A28-B25, B8, and DR3.^{20,21,41,57} Other studies, however, refute any association of HLA class II genes with EHBA.^{35,58} Analyses have examined the possibility that biliary ductal epithelial cells are susceptible to immune attack because of the abnormal expression of HLA class I molecules at the cell surface.^{59,60} Others have suggested that this susceptibility is because of the abnormal expression of inflammatory adhesion molecules.⁵⁹ Regardless of genetic predisposition, however, the inciting variable that serves as a trigger for the injury has not been identified.

Recently, the possibility that EHBA is a phenotypic end product of multiple different insults and potentially divergent mechanisms has been entertained. In this case, the infant liver has responded with inflammation, bile duct proliferation, apoptosis, and fibrogenesis to a variety of injurious stimuli.⁸ Furthermore, these insults may be occurring not only simultaneously but also both antenatally and perinatally. These processes are both dynamic and complex. The abundance of studies implicating different primary triggers for the biliary duct obstruction underlying EHBA suggests that the pathogenesis is multifactorial. The genetic, inflammatory, and infectious factors likely all play a role, but the timing and characterization of the interplay between these factors remain unclear.

Our current treatments focus on the symptomatic outcomes of the disease, not its underlying cause. Further understanding the pathogenesis of EHBA is a critical step in the development of new and more effective treatment strategies aimed at stopping the bile duct injury before its clinical consequences.

CLINICAL FEATURES

In infants with EHBA, their birth weight and gestation are usually normal. As EHBA is a condition that progresses over time, many infants develop the clinical signs and laboratory abnormalities over weeks. Presenting features usually include icterus, dark urine, and pale stools by 4 to 6 weeks of age in an otherwise thriving infant. Depending on the extent of the

disease at diagnosis, hepatosplenomegaly is commonly present reflecting portal hypertension. Some cases present early with bleeding owing to vitamin K malabsorption and deficiency. Prolonged neonatal jaundice beyond 2 weeks of age and identification of primarily conjugated hyperbilirubinemia frequently raise the index of suspicion for the condition.

Laboratory values are notable for a moderate-conjugated hyperbilirubinemia, striking elevation of γ -glutamyl transferase, and mildly to moderately elevated serum transaminases. The conjugated bilirubin level is usually less than 7 mg/mL and is typically 50% to 80% of the total bilirubin.⁸

As stated earlier, although EHBA is an isolated abnormality in most infants, 10% have other visceral and vascular abnormalities, and consequently it is important to evaluate patients for these important associated anomalies.

DIAGNOSIS

The diagnosis of EHBA is sometimes challenging. There is a high degree of overlap in clinical, radiologic, and histologic characteristics of EHBA with other causes of hepatitis in the neonate. This is further complicated by the urgency of EHBA diagnosis. The diagnosis of EHBA before 60 days of age is essential so that a portoenterostomy can be performed with the highest rates of success. The differential is broad and includes structural, genetic, infectious, and metabolic conditions (Table 1). Unfortunately, there is no single preoperative test that can diagnose EHBA with certainty. However, with a combination of investigations it is possible to be reasonably certain in most cases. The testing algorithm is somewhat variable between major referral centers, but the basic approach standard⁶¹ (Table 2).

In some countries, infant screening for biliary atresia has been initiated using stool color cards. The parents are asked to return the card tracking the infant's stool color for physician evaluation at the 1-month routine visit.⁶² The efficacy of this screening tool has not yet been proven, but the specificity is low.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guideline for evaluation of cholestatic jaundice in infants recommends that any infant noted to be jaundiced at the 2-week well child visit should be evaluated for cholestasis.⁶³ The evaluation of breast fed infants, however, may be delayed until 3 weeks of age if they have normal physical examination, no history of dark urine or light stools, and can be reliably monitored.⁶³ If the infant has direct hyperbilirubinemia (>15% of the total) at either of these times, then causes of cholestatic jaundice should be investigated. It is of utmost importance to quickly exclude any treatable disorders so that treatment is not delayed. This initial evaluation should include a complete history including previous medical issues, neonatal infection, history of ABO hemolytic disease, prenatal ultrasound and results, weight gain, dietary history, stooling pattern, stool color, urine color, and complete family history. A complete physical examination should also be performed at this time. The laboratory studies that should be carried out to assess liver cell injury and biliary disorders include total and conjugated bilirubin, serum alanine aminotransferase, serum aspartate amino-transferase, serum alkaline phosphatase, and γ -glutamyl transferase. Other

studies include a complete blood count, urinalysis with testing for reducing substances (if on a galactose-containing diet), glucose, prothrombin time, albumin, thyroid function tests, bacterial culture of urine and blood, A1AT level and genotype, and screening for cystic fibrosis.

Several radiological studies may also assist in the diagnosis, and have been used in the evaluation of EHBA. These include hepatobiliary ultrasonography, hepatobiliary scintigraphy, magnetic resonance cholangiopancreatography (MRCP), and rarely endoscopic retrograde cholangiopancreatography (ERCP). Evaluation of biliary anatomy often begins with an ultrasonography. In EHBA, the absence of a gallbladder and the presence of the triangular cord sign (triangular or band-like periportal echogenic density >3mm in thickness) may be found.^{64, 65} The sensitivity and specificity of a small or absent gallbladder in detecting EHBA runs from 73% to 100% and from 67% to 100%, respectively when correlated with clinical, pathologic, and subsequent surgical evaluations. Several reports suggest that the triangular cord sign may be more useful in diagnosis with the sensitivity and specificity ranging from 83% to 100% and from 98% to 100%, respectively.⁶³ Failure to visualize the gallbladder may be the result of gallbladder collapse or an inexperienced ultrasonographer, however.

Hepatobiliary scintigraphy (HBS) has been used over the last 20 years to aid in the differentiation of EHBA from other causes of conjugated hyperbilirubinemia that do not need early surgery.^{66–68} The reported sensitivity of HBS is high, often 100%, but the specificity is lower and variable, ranging from 40% to 100%.^{66–71} The tracers found to have the best hepatocyte extraction and less renal excretion is either Tc-99mDISDA (diisopropyl-iminodiacetic acid) or Tc-99m mebrofenin (trimethylbromo-iminodiacetic acid).⁶⁶ Improved sensitivity and specificity have been reported if the patient is premedicated with phenobarbital for 5 days, and when delayed imaging is performed at 4 to 6 hours and at 24 hours^{66–68} when earlier biliary excretion is not visualized. A recent publication reported using premedication with ursodeoxycholic acid before HBS. Poddar et al⁷² described improved specificity from 54.3% to 88.6% in this group. Another recent study demonstrated specificity increase from 67% to 97% with the addition of single photon emission computed tomography, 4 to 6 hours postinjection of tracer. Remarkably, in this study, the addition of single photon emission computed tomography increased the specificity to 90%, without the use of phenobarbital premedication. Given the time constraints of diagnosis, this may be quite beneficial as proper phenobarbital premedication delays the investigation.⁷³

Liver biopsy is often considered the gold standard for the diagnosis of EHBA. According to one report, it is accurate in 96% to 98% of cases, provided that the specimen contains at least 5 to 7 portal spaces.⁷⁴ Review of further studies revealed that EHBA is diagnosed correctly by liver biopsy in only 50% to 99% of the cases and EHBA is erroneously diagnoses from biopsy review in 0% to 46% of cases.⁶³ The accurate diagnosis using liver biopsy is limited by pathologist experience and the dynamics of the disease. For example, specimens obtained early in the course of EHBA may be indistinguishable from neonatal hepatitis,⁷⁵ with the biliary hyperplasia not yet obvious, and if too late the damage will be too severe for accurate diagnosis. Common histologic findings include fibrous portal expansion, an increased number of intralobular bile ducts, and ductal proliferation.³ Portal

inflammation is visible, and also intrahepatic cholestasis. The portal fibrosis varies from portal expansion to cirrhosis. The Cholestasis Guideline Committee recommends that a liver biopsy be performed in most infants with undiagnosed cholestasis, to be interpreted by a pathologist with experience in pediatric liver disease.⁶³ Although many centers carry out a percutaneous liver biopsy before any surgical intervention, the variable sensitivity and specificity of these biopsy results depending on the stage of disease evolution has lead many centers away from percutaneous biopsies in favor of carry out the biopsy at the time of a diagnostic intraoperative cholangiogram.

The data supporting the use of ERCP for the diagnosis of EHBA are sparse. Ohnuma et al⁷⁶ performed ERCPs in 73 infants with cholestasis, and EHBA was diagnosed in 47 patients. The usefulness for ERCP appears to be center and operator dependent. MRCP has been evaluated as another potentially helpful tool for diagnosing EHBA. Results from initial studies are encouraging.⁷⁷⁻⁸⁰ In 2 studies,^{77,79} the negative and positive predictive values of MRCP in detecting EHBA were from 91% to 100% and from 75% to 96%, respectively. MRCP is a noninvasive study with a highly accurate diagnostic rate by experienced radiologists. It is anticipated that this diagnostic tool will become more widely used as it is increasingly available and comfort with its use increases.

As may be obvious from this discussion, the diagnosis of EHBA is sometimes difficult and may be incorrect in some cases. There is a high degree of overlap in clinical, radiological, and histologic characteristics of EHBA and other causes of hepatitis in the neonate. It is likely that a number of infants who carry a diagnosis of EHBA may actually have another disorder of the biliary system that has clinical characteristics that overlap with EHBA, including Alagille syndrome, Caroli disease, congenital hepatic fibrosis, neonatal sclerosing cholangitis, and variants of intrahepatic biliary ductular hypoplasia syndromes.^{9,81,82}

TREATMENT

Current treatment of EHBA is surgical. Hepatopertoenterostomy for the relief of biliary obstruction in these infants was initially reported in 1959 by Kasai.¹⁷ Now commonly called the Kasai procedure, it consists of mobilizing the extrahepatic biliary tree and anastomosing a jejunal Roux en-Y loop to the liver hilum. If successful, any patent intrahepatic bile ducts will drain into the roux limb allowing relief of the biliary obstruction. If possible, a Kasai procedure should be performed before 60 days of age when its short-term success is 80%.^{16,83,84} Efficacy of the procedure drops with age of the patient, decreasing to 60% by 90 days of age. Although the prognosis is worse and the need for transplantation is higher in infants who undergo the Kasai procedure after 3 months of age, most hepatologists feel the procedure should be attempted in most of these patients. Overall, 20% to 30% of patients who undergo a Kasai for EHBA enjoy long-term stability of their disease.^{84,85} However, even if the biliary obstruction is successfully treated via the Kasai operation, ongoing lifelong management of the disease is usually required, and aggressive nutritional support with correction of nutritional deficits is likely to improve outcome.^{82,86-92}

Several approaches have been used to attempt to enhance bile drainage after the Kasai procedure. These include the use of choleretics, such as ursodeoxycholic acid and

phenobarbital, bile acid and binding resins, and anti-inflammatory drugs.^{93,94} Unfortunately, the clinical trials have been limited and it is not yet known whether these measures are beneficial. The use of steroids perioperatively, to decrease the inflammatory response that is known to play a role in the destructive biliary pathogenesis, and that could be exacerbated by the surgical intervention, is a current focus of multicentered research. Recent evaluation does not support the use of oral steroids⁹⁵ but there are currently no placebo-controlled studies powered well enough to definitely answer the question of whether perioperative steroids are beneficial. BARC is currently performing the definitive study to answer this question (<http://www.barcnetwork.org/>).

Liver transplantation is performed when biliary flow is not restored and synthetic dysfunction or complications of biliary cirrhosis occur.⁹⁶

OUTCOME

With the sequential treatment interventions of a Kasai portoenterostomy and secondary liver transplant, if required, overall survival rate is approximately 90%.⁹⁷ Survival with the native liver after the Kasai operation is approximately 30% of the patients at 10 years and 14% to 23% at 20 years.^{16,84,98,99} Several prognostic factors of success of the Kasai procedure have been identified. Currently, these include the anatomy of the extrahepatic biliary remnant, age at Kasai procedure, occurrence of postoperative cholangitis, presence of cirrhosis, experience of the hospital in the management of EHBA patients, and presence of liver fibrosis at the time of the Kasai procedure.^{6,14,16,85,94,98,100–110} A longer duration of jaundice before the Kasai procedure, failure to establish bile flow, requirement for phototherapy in the neonatal period, and portal plate ductules smaller than 200 μm have also been shown to be associated with the need for liver transplant after the Kasai procedure.¹¹¹

Duche et al¹¹² recently demonstrated that elevated portal pressure at the time of the Kasai procedure was significantly related to a higher risk of developing portal hypertension in infancy and childhood, even if bilirubin levels normalize after the operation. Interestingly, the measurement of portal pressure in this study was a better predictor of postoperative outcome than the histologic scores of liver fibrosis.

In a large multicenter study, the anatomical pattern of the extrahepatic biliary remnant was also shown to be related to the success of the Kasai operation. Ten-year survival with native liver decreased from 83% in atresia limited to the common bile duct to 56% in atresia with a cyst in the liver hilum communicating with dystrophic intrahepatic ducts, 36% in biliary atresia with a patent gallbladder, cystic duct, and common bile duct, and 21% in complete EHBA.¹⁶ Thus, the severity of intrahepatic lesions is likely associated with severity of the extra-hepatic lesions, and that a worsening prognosis is associated with a higher degree of EHBA.

Cholangitis is an important complication of the Kasai procedure, particularly where the operation has restored bile drainage. It is seen in 45% to 60% of the patients.^{113–117} More than half of these infants have their episode of cholangitis within the first 6 months in most series and 90% within the first year.^{113,117,118} The frequency is much reduced in later childhood and adolescence but continues to affect a small proportion. In a report of long-

term (>20 y) survivors of the Kasai procedure, 10 (50%) of 21 had an episode of cholangitis in the previous 5 years.¹¹⁹ Three main mechanisms for the occurrence of cholangitis have been suggested: bacterial translocation via lymphatics,^{120,121} hematogenous spread via the portal venous system,¹²² and luminal colonization via the Roux loop. Despite the theories, however, there has been almost no evidence to definitely clarify the mechanism of the post-Kasai cholangitis.

Intrahepatic cystic lesions have also been seen to develop after hepatic portoenterostomy. Reported incidence has ranged from 18% to 25%.¹²³⁻¹²⁸ Their occurrence has generally been regarded as a sign of poor prognosis.¹²³⁻¹³⁹ Tainaka et al¹²⁷ recently separated these intrahepatic cystic lesions into solitary simple lesions and continuous or beaded cystic lesions by imaging studies, which also showed a difference in histological and clinical features. They found prognosis to be poor in patients with solitary liver cysts, with most patients requiring liver transplantation. Clinical improvement was generally seen in patients with continuous beaded cystic lesions, however, and this condition is generally believed to be reversible.

The development of hepatocellular carcinoma in EHBA is rare. Only 13 cases are reported in the literature, including 7 children treated with a liver transplantation.^{140,141} This association is assumed to be more common than is documented, however, as children with cirrhosis are at risk in general for hepatocellular carcinoma.

Even when the Kasai procedure successfully restores bile flow, progressive inflammation and fibrosis of the intrahepatic bile ducts, exacerbated by cholestasis and cholangitis, still develops in many patients, leading to biliary cirrhosis and the need for liver transplantation in 70% to 80% of patients eventually.^{13,85} Barshes et al¹⁴² recently evaluated the outcome of liver transplantation in a large group of 1976 pediatric patients who received a liver transplant between 1988 and 2003. The 1-year, 5-year, and 10-year survivals for these patients were 90.0%, 87.2%, and 85.8%, respectively, and the 1-year, 5-year, and 10-year graft survival rates were 83.6%, 76.2%, and 72.7%, respectively. These data clearly demonstrate the effectiveness of liver transplantation as a treatment for EHBA. Early deaths (<90 d posttransplant) were most commonly caused by graft failure whereas late deaths (>90 d) were more often caused by malignancy. Furthermore, it has been demonstrated that previous Kasai procedure does not predict patient survival postliver transplant.⁸² This further validates the current practice of staged treatment for EHBA.

With the organ demand for liver transplantation higher than the cadaveric-donor organ availability, living donor transplantation has become more common and is frequently offered to pediatric and adult patients with EHBA. In a recent series review,⁹⁶ the outcome of adult-to-adult living donor liver transplantation for post-Kasai EHBA was examined. It was observed that the adults had significantly lower 10-year survival rate (52% vs. 80%) compared with children. It was also found that the incidences of intestinal perforation (31.9% for adults vs. 8.4% for pediatric populations) and intra-abdominal bleeding requiring laparotomy for hemostasis (27.7% vs. 9.6%) were also both significantly higher in adult populations.

A recent retrospective review of 9 centers participating in BARC⁶¹ showed that there is no standard approach to the diagnosis of biliary atresia and the postoperative management varies greatly. Despite this, however, the patient outcomes at age 2 years for all 9 centers were comparable with the best outcome data published from other countries and in large single-center reports.^{16,85,104,143,144} It was also found that a total serum bilirubin level <2 mg/dL in the months post-Kasai correlated strongly with good outcome at 2 years, whereas serum bilirubin >6 mg/dL at 3 months post-Kasai predicted poor outcome.

The importance of evaluating children with EHBA for possible congenital anomalies is underscored by their long-term prognosis as the survival and clinical course for infants with syndromic EHBA is often negatively affected by the associated anomalies. Cardiac anomalies, for example, can be immediately life threatening. These children have also been noted to have increased risk of clinically significant hepatopulmonary syndrome, which may lead to sudden death.¹⁴⁵ Most studies have found infants with associated anomalies to have much lower 5-year native liver survival,^{16,61,97,146} although some others have found to have no difference in short-to medium-term outcome.^{147,148}

CONCLUSIONS

EHBA is a rare disease that remains the most common indication for liver transplantation in children. Recently, our understanding of both etiology and pathogenesis of EHBA has rapidly improved, although much remains unclear. It is possible that there is a common mechanism connecting the inflammatory, viral, and genetic theories of pathogenesis or multiple mechanisms leading to the clinical diagnosis of EHBA. The current surgical treatments of hepatoportoenterostomy and liver transplantation have improved the outcomes greatly. These treatments, however, focus on repairing the outcome of EHBA. It is hoped that as the underlying pathogenesis is further elucidated, those treatments may be created which instead focus on halting disease progression.

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TABLE 1**Differential Diagnosis of Neonatal Cholestasis**

Anatomic or obstructive cholestatic disorders
Choledochal cyst
Bile duct stenosis
Sclerosing cholangitis of the newborn
EHBA
Cholelithiasis
Tumors/masses
Infectious
Viral: adenovirus, enterovirus, hepatitis (A, B, C, D, and E), herpes virus, HIV, reovirus, rubella, and parvovirus
Bacterial: sepsis, urinary tract infection, syphilis, and tuberculosis
Metabolic/Genetic
Alagille syndrome
Disorders of amino acid metabolism
Disorders of glucose metabolism: galactosemia, fructosemia, glycosylation defects, glycogen storage disease type IV
A1AT deficiency
Cystic Fibrosis
Mitochondrial disorders
Toxic
Parenteral nutrition
Drugs

TABLE 2

Diagnostic Evaluation in the Cholestatic Neonate

Basic evaluation
Serum aspartate aminotransferase and Serum alanine aminotransferase
γ -glutamyl transferase
Bilirubin—indirect and direct
Prothrombin time/International normalized ratio
Albumin level
Complete blood count
Initial diagnostic evaluation
Blood and urine cultures
Urine for reducing substances (if infant on a galactose-containing diet)
Galactose-1-phosphate uridyl transferase
Urine succinylacetone
Thyroid-stimulating hormone/T4
Cortisol
Hepatobiliary ultrasound
Secondary diagnostic evaluation
A1AT level and genotype
Cystic fibrosis screen
Liver biopsy
Hepatobiliary scintigraphy
MRCP or ERCP (depending on facility)