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Review

Biliary Atresia: A Systematic Review of Etiology, Pathogenesis, Diagnosis and Treatment

Moreno Alfonso Julio César*, Poblador Pérez Misael, Suarez Amaya Miguel Alejandro, Barrera Orozco Estefanía Marina, Cárdenas Parra Karen Lorena, Ávila Benavides Paula Andrea and Montaña Africano Paola Andrea

Surgery Resident, Spain

Correspondence to: Julio César Moreno Alfonso; Surgery Resident, Spain; E-mail: juliomoreno.md@gmail.com

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ABSTRACT

Biliary Atresia (BA) is an uncommon, progressive and idiopathic fibro-obliterative cholangiopathy. The typical clinical features should be identified prompt in order to realize a Kasai Hepatoportoenterostomy (HPE) for restore the bile flow. However, despite HPE the BA remains the most common indication for liver transplantation in children. The lasts studies have shown the importance of virus, immunity and other environmental substances in pathogenesis of BA that is important in order to look for new therapeutic and preventive strategies. This article is a systematic review of the literature about actual evidence in BA.

Keywords: *Biliary atresia; Neonatal jaundice; Kasai hepatoportoenterostomy; Liver transplantation.*

INTRODUCTION

Biliary atresia (BA) is a progressive, idiopathic, fibro-obliterative disease of intrahepatic and extrahepatic bile ducts leading to obstructed bile flow, cholestasis, liver fibrosis and cirrhosis. It debuts in the neonatal age with persistent jaundice, pallor stools and hepatomegaly. If untreated it is fatal with a survival <10% at 3 years of age.[1-9]

First reported case of this condition was in 1817 by Dr. John Burns, he described an incurable disease of bile ducts. Later, the first surgical success was achieved by Dr. William Ladd´s in 1920; however, BA continued to have a somber outcome until the 50´s when Dr. Morio Kasai described the Kasai Hepatoportoenterostomy (HPE) through dissecting the proximal obstructed bile duct and making a Roux-en-Y loop that is today the standard procedure for all children undergoing surgical correction. Liver transplantation is an option to children who have either failed to restore the bile flow in Kasai procedure or have advanced cirrhosis.[1,10]

SEARCH STRATEGY

An UpToDate, DynaMed, Europe PMC, Biblioteca Virtual en Salud (BVS), Google Scholar and PubMed search was carried out with the following Medical Subject Headings (MeSH) terms: "*biliary atresia*", "*bile duct atresia*", "*intrahepatic biliary atresia*" and "*extrahepatic biliary atresia*". All relevant and non-duplicated review articles published in English and Spanish in the last five-year period were included in this review.

EPIDEMIOLOGY

The overall incidence is approximately 1/10.000-20.000 live births, there are regional variations of BA with a higher incidence in Taiwan and Japan about 1-5/1.000, lower one in England 1-5/20.000, United States and Europe 5-6/100.000, some studies has shown seasonal variability and slight female predominance. BA is the most common indication for liver transplantation in children and accounts for 33% to 50% of neonatal cholestasis.[2-12]

ANATOMY

Usually, intrahepatic bile ducts collect bile from liver and become confluent for each liver segment, further confluence at level of hilum plate results in formation of extrahepatic bile ducts. Normally, left hepatic duct is formed by ducts from hepatic segments II, III and IV. Right hepatic duct is formed by ducts from segments V, VI, VII and VIII of the liver, outside of liver parenchyma right and left hepatic ducts join to form common hepatic duct. The cystic duct from gallbladder joins with hepatic duct to form common bile duct and this flow in second duodenal portion. Variations in biliary anatomy are common.[3]

ETIOLOGY AND PATHOGENESIS

The etiology of BA is unknown. Theories suggest multifactorial etiologies that leading to abnormal embryogenesis or ductal inflammation, injury and necrosis result in progressive fibrosis of intrahepatic and/or

extrahepatic bile ducts. Around 3% to 20% of children with BA have some associated syndrome or congenital anomaly; therefore it is likely that some genetic component is present in the pathogenesis because no single factor has been associated so far. A few familial cases are described and there no increase in the incidence has been note in twins, some investigators pose that BA begins in the uterus.[1,3,5,8,13]

Viral

Several viral agents such as reovirus, rotavirus, human papilloma virus, Cytomegalovirus (CMV), respiratory syncytial virus and others have been involved in the past but there is not a specific association, however, a study of 249 patients with BA over 16-year period in New York State demonstrated seasonal behavior of incidence relative to region in the state, children born in spring in New York City had highest risk of BA, whereas outward city children born in autumn months had a higher risk. Children with positive CMV immunoglobulin M (IgM) can to have reduced clearance of jaundice after Kasai surgery.[2,9,10,14-17]

Toxics

The toxic hypothesis comes from three reported outbreaks in Australia (1964, 1988 and 2007) when ewes that gave birth to affected lambs had grazed on lands with Dysphania plant in which a new isoflavonoid toxic (biliatresone) was isolate. Blithesome is able to cause severe damage to extrahepatic biliary ducts, all this suggest that an environmental toxin may be associated in some cases of BA.

Genetic

Genetic factors may be associated in subgroup of patients with BASM.

A CFC 1 gene mutation, which encodes cryptic protein and is involved in determining laterality during embryogenesis, have been associated with BASM syndrome. A heterozygous mutation in CFC1 was found in 5 out of 10 infants with BASM. This mutation may predispose to BASM but is not sufficient to cause the syndrome.

Heterozygous or biallelic variants of PKD1L1 (policystin 1-like 1) gene have been found in some cases of BASM. PKD1L1 is expressed in primary cilia and is involved too in determination of laterality.

A genomic-wide study identified EFEMP1 as a candidate susceptibility gene for BA. EFEMP1 encodes an extracellular matrix protein expressed in cholangiocytes and portal fibroblasts.

Analysis of BA cases in Caucasian and Asian cohorts have identified a risk locus on Chromosome (Ch) 10q24.2, the ADD3 gene (adducin 3), follow-up studies have demonstrated that alterations of ADD3 expression influence risk for BA; loss of ADD3 in a zebrafish model leads to anomalies in biliary developmental.

Heterozygous deletion of the FOXA2 gene (forkhead box 2A) has been notified in a family with heterotaxy, panhypopituitarism and BA.

Some subgroups of patients with BASM, genetic factors may not have a direct causative role in the development of most cases of BA; this is suggested by the observation that monozygotic twins usually have a discordant phenotype.

Epigenetic factors have also been postulated as important factors impacting biliary development and the pathogenesis of BA.

Others genic alterations related to BA are mutation in jagged 1, HNF-6, inversing gene in Ch4, polymorphism of Vascular Endothelial Growth Factor gene (VEGF), microRNA-222 over expression and aneuploidy of Ch 22 in cat-eye syndrome.[2,6,8,14,18]

Immunologic

Immune disorder, either as primary or as result of infectious or genetic triggers, has been associated in various studies. Abnormalities in innate immunity, cellular immunity and humoral immunity have been identified in human samples and mouse models. Interleukin 17a (IL17a) has recently been shown to promote macrophage recruitment that may be important in the progression of the liver and duct injury. Children with BA had a higher level of IL17a-positive cells in liver samples compared with normal and cholestatic controls.

A high concentration of maternal chimeric cells has been found in the portal and sinusoidal areas of patients with BA, supporting that maternal lymphocytes cause bile duct injury through a graft-versus-host immune response.

Activation of genes related to lymphocyte differentiation, particularly those associated with helper 1 immunity, has been identified in liver samples from children with BA.

Polymorphisms that enhance expression of the CD14 gene, which plays a role in the recognition of bacterial endotoxin, have been associated with BA and idiopathic neonatal cholestasis.[2,5,6,10,11,17,18]

CLASSIFICATION

Based on Timing of Onset

Postnatal biliary atresia (65% to 90%): Usually an isolated disease.

Embryonal or fetal biliary atresia (10% to 35%): Most cases associated with other congenital malformations, may also be associated with cystic dilatation of biliary remnants.

Based on syndromic and non-syndromic varieties:[1-3]

Isolated Biliary Atresia or Perinatal

Represents the most frequent type (70% to 85%), etiology is unknown. Frequently these children are born without jaundice and develop it within the first two months of live and stools become acholic progressively.

Biliary atresia splenic malformation syndrome (BASM) or embryonal BA: Occurs in 10% to 15% of infants with BA, is associated with asplenia or polysplenia, vascular malformations (pre-duodenal portal vein, interrupted inferior vena cava, azygous continuation), cardiac anomalies, intestinal malrotation and situs inversus. In this case the malformations occur early in embryogenesis and explain the other abnormalities. Is most frequent in maternal diabetes and have female predominance. Infants with BASM have poorer outcomes compare with those with perinatal BA.

BA in association with other congenital malformations: This occurs in 5% to 10% of BA cases. Associated congenital malformations include kidney anomalies, imperforated anus, intestinal atresia and/or heart abnormalities.

Cystic biliary atresia: There is an obliteration of the bile ducts with cystic dilatation, the incidence is around 10%, it has better prognosis.

CMV IgM (+) Biliary atresia: Prevalence is around 10% of the cases, most of them are non-caucasians. Usually these children have higher bilirubin and AST levels and more inflammation cells in extrahepatic

bile ducts. This type has the worst prognosis.

Based on Morphological Classification

Based on the level of obliteration of bile duct the Japanese Association of Pediatric Surgeons classified it as:

Type I (5% to 12%): Obliteration of the common bile duct.

Type IIa (2%): Obliteration of the common hepatic duct.

Type IIb (2%): Obliteration of the common bile duct, hepatic duct, cystic duct without anomalies of the gallbladder and cystic dilatation at the porta hepatis.

Type III (86% to 90%): Obliteration of the common bile duct, hepatic duct and cystic duct with no anastomosable ducts at the porta hepatis. This is the most common type.

CLINICAL PRESENTATION

Children with BA usually are born at full term, have a normal birth weight and appear healthy. Patient presents in the neonatal age with persisting jaundice(first sign) that occurs any time from birth up to eight weeks of age, clay-colored stools, dark urine, splenomegaly and hepatomegaly, therefore, any child with jaundice >14 days should undergo evaluation. More than 50% of the children with BA will have normal stools initially that later become acholic. As the disease progress appears signs of liver cirrhosis and failure, splenomegaly, ascites, signs of portal hypertension, among others.[1-5]

EVALUATION

A child with conjugated hyperbilirubinemia and clinical features that suggest BA should undergo for several test and multidisciplinary management as rapidly as possible regarding the success of the Kasai procedure diminishes progressively with older age at surgery.

Laboratory Studies

In BA conjugated (predominantly) and unconjugated bilirubin levels are elevated, alkaline phosphatase levels are elevated usually in children due to bone remodeling, so, liver-specific alkaline phosphatase fraction 5´nucleotidase level should be measured. Gamma Glutamyl Transpeptidase (GGTP) is increased in case of biliary obstruction, it provides a diagnostic accuracy of 50-60% in BA. Cholestasis is defined as conjugated bilirubin >1mg/dL when Total Serum Bilirubin (TSB) ≤ 5mg/dL or >20% of TSB if >5mg/dL. Aminotransferases levels may be mildly elevated. Preclinical dates suggest that elevated serum levels of matrix metalloproteinase-7 (MMP-7) may be useful for distinguish BA from other causes of neonatal cholestasis, with positive and negative predictive values above 90%.[2] Another study include coagulation test, assessment of synthetic function of liver, genetic testing, viral serologies and cultures if infectious etiology is suspect.

Imaging Studies

Ultrasound: Ultrasonography (US) is an available and noninvasive test that can provide valuable information regarding vascular patency, ascites, surface and anatomy liver; and can also exclude other causes of obstructive jaundice (choledochal cyst, liver masses, among others). US usually shows hypoplastic or absent gallbladder, absence of intrahepatic biliary ducts, hepatic subcapsular flow sign,[19] it can identify the triangular cord sign described by Park et al (echogenic density just above-porta hepatis).In antenatal period BA can be detected with maternal US around 20 weeks' gestation, this can facilitate an early postnatal treatment. The diagnostic accuracy of US for BA is 78%.[1-3]

Hepatobiliary scintigraphy: It used Technetium labeled compound di isopropyl iminodiacetic acid (DISDIA). Presence of isotope in the intestine excludes BA. The test reliability decreases in presence of high levels of conjugated bilirubin. The false-positive and negative rate is 10%, therefore, if excretion is noted on imaging test performed when the infant is very young (<6 weeks) and cholestasis persists, the scan should be repeated one to two weeks later because the disease may progress in neonatal period. Administration of phenobarbital (5 mg/kg/day) for 5 to 7 days prior to scan can increase specificity.[1-3]

Duodenal intubation: The aspiration of bile-stained fluid from duodenum will rule out BA, this is an invasive and not widely performed test.

Magnetic resonance imaging (MRI) and Magnetic resonance cholangiopancreatography (MRCP): MRI and MRCP is accuracy test but not usually performed due to expense and requirement sedation.

Endoscopic retrograde cholangiopancreatography (ERCP): ERCP is used in case that other test has failed to confirm the diagnosis. Not widely done due to the limited availability of neonatal scopes equipped.

Liver biopsy: It can differentiate BA from other causes of cholestatic jaundice with a high accuracy level. Findings suggest BA include: Bile duct proliferation (most sensitive and specific), bile plugging, multinuclear giant cells, cholestasis, portal tract fibrosis, focal necrosis of liver parenchyma and inflammatory cell infiltrate. Biopsies done too early may result in false negative because earliest histologic changes may be nonspecific. At times, it is necessary to repeat a liver biopsy at an older age (1-3 weeks later).[1-4]

Cholangiogram: If previous tests support the diagnosis of BA, the infants should be taken to the operating room. The first step is an intraoperative cholangiogram, which is the gold standard in the diagnosis of BA. If biliary obstruction is demonstrated (contrast does not fill the biliary tree or reach the intestine), a Kasai procedure is indicated. A valid alternative is to perform a percutaneous gallbladder cholangiogram.

DIAGNOSIS

BA should be suspected in case of neonatal conjugated hyperbilirubinemia and/or acholic stools supported by results of a variety of test (ultrasound, hepatobiliary scan and liver biopsy). Definitive diagnosis is made by intraoperative cholangiogram.[1-3,20]

DIFFERENTIAL DIAGNOSIS

- Alagille syndrome
- Alpha 1 antitrypsin deficiency (10% of neonatal cholestasis)
- TORCH (Toxoplasma, others, rubella, cytomegalovirus, herpes simplex virus)
- Caroli´s disease
- Choledochal cyst
- Autoimmune, idiopathic or infectious neonatal hepatitis (10% to 15% of neonatal cholestasis)
- Lipid metabolism disorders

- Sepsis
- Total parenteral nutrition-associated hepatitis

TREATMENT

Surgical exploration is the only way for accurately diagnose and to treat BA.

Peri-operative Cholangiogram

Peri-operative cholangiogram will definitively diagnose BA if dye do not passage into the intra and extrahepatic biliary system.

Kasai Procedure, Hepatoportoenterostomy (HPE)

The standard surgical technique is the Kasai procedure, that consists in to create a Roux-en-Y hepatic portoenterostomy with excision of the fibrotic biliary remnant, transaction of the fibrous portal plate with dissection extending up to the bifurcation of the portal vein, the goal is reestablish biliary-enteric drainage, the success rate is around 60%, patients are less likely to require liver transplantation if surgery is performed within 10 weeks of life, however, at least 50% of children who undergo HPE will require liver transplantation by two years of age as a result of primary failure of the HPE and/or growth failure. Patients which undergo HPE ≤ 30 days of life the chance of native liver survival at four years of age is nearly 50%, however in those who underwent HPE between 31-90 days of life, the chance of native liver survival at four years of age is 36%.[1-4]

If HPE is unsuccessful, bile flow is not achieved and the child remains jaundiced. If there is persistent jaundice or elevated serum bilirubin three months after the procedure, the infants should be referred for liver transplant evaluation. In general terms revision of nonfunctioning HPE is not recommended because is unlikely to be effective and may cause adhesions that increase the technical difficulty of a subsequent transplant procedure. However, if after successful HPE abruptly appears jaundice or recurrent episodes of cholangitis without evidence of other chronic liver disease revisional HPE may be appropriate because up to 75% achieved bile drainage.

If bile drainage is achieved, it is likely that transplantation will not be needed for years or decades.

HPE should be always the first surgical treatment. Preemptive transplant (transplant without prior HPE) is not recommended because the advantages of transplanting older, larger patients and with modernest transplantation techniques. A systemic review and meta-analysis that compares the effectiveness of Laparoscopic HPE (LPE) versus open HPE (OPE) found no significant difference between the two groups in operative time, hospital stay, intraoperative blood loss, early clearance of jaundice, cholangitis and variceal bleeding, moreover, the rate of 2-year survival with native liver was significantly high in OPE group than in LPE one. Therefore, OPE remains the gold standard in the treatment of BA,[21] however, some center use LPE as choice procedure for BA.[22] Perioperative mortality is reported around 1% to 2%.[23]

Postoperative Management

Postoperative medical care consists in:

Choleretics

A standard practice in BA is to administrate Ursodeoxycholic acid (UDCA) after Kasai HPE, although its clinical utility has not been definitively established. UDCA is a hydrophilic bile acid that shifts the balance of bile acids towards hydrophilic forms, therefore, is thought to stabilize membranes and reduce free radicals' generation, thus protecting mitochondria from damage. Recommended dose ranges from 15 to 30 mg/kg/day. In order to avoid potential toxicity, UDCA should be discontinued if the total bilirubin level arises above 15mg/dL. In patients with primary biliary cholangitis UDCA decreased plasma levels of aminotransferases, improved liver histology and quality of life and decreased risk of death and need for liver transplantation. In BA UDCA enhanced weight gain, reduced episodes of cholangitis and improve bile flow (observational studies).[2]

Glucocorticoids

There is not clinical evidence to support routine use of glucocorticoids in the treatment of BA because no statistically significant benefit in bile drainage, survival with native liver was observed, moreover the children treated with glucocorticoids had earlier onset of serious adverse events.[3,24]

Nutrition

Nutritional problems in BA are common and difficult to overcome; in fact, it is a significant clinical problem and one of the most common indications for liver transplantation.

Caloric Needs

Several factors (malabsorption due to cholestasis, liver inflammation and lack of gallbladder) contribute to malnutrition in patients with BA. Because of malabsorption and metabolic disorders, the caloric needs in infants with BA are around 130-150% of the recommended energy intake for healthy infants and children, to compensate for losses and catabolism, the expected protein needs are 2-4 g/kg/day. There are several strategies to achieve nutritional requirements.

For infants, formulas are concentrated or expressed breast milk is fortified to provide additional energy. After HPE, the feed is typically designed to provide 24kcal per ounce, if growth is inadequate, the feed may be increased to 27kcal per ounce, additional energy content can be added in solid foods when the infant is old enough.

High-energy supplements, like glucose polymers or medium-chain triglyceride (MCT) oil are used to fortify formula solid foods. MCT is especially useful because it is calorically rich and easy to absorbed by patients with cholestasis because it does not require micellar solubilization. In order to avoid essential fatty acid deficiency, long-chain triglycerides (LCT) should be included (at least 3% of total calories). If despite this supplementation there is not poor weight gain and/or poor linear growth nasogastric tube should be considered.[2-4]

Fat-Soluble Vitamin Supplements

All infants with jaundice and children with BA should to received supplements of fat-soluble vitamins (vitamin K, E, D and A). When jaundice resolves and vitamins are replete, children can be transitioned to standard multivitamins with routine monitoring of vitamins levels because vitamin deficiencies occur despite recommended supplementation specially in patients with residual cholestasis after HPE.

Liver Transplantation

BA is the most common indication for liver transplantation in infants and children. At least 60% to 80% of patients with BA will require liver transplantation, even with HPE and optimal management.

Indications for liver transplantation in patients with BA include:[1,2,25]

- Primary failure (lack of drainage) after HPE.
- Early referral for liver transplantation if total bilirubin is >6 mg/dL three months or more beyond HPE.
- Referral for liver transplantation evaluation also should be considered if total bilirubin is persistently 2-6 mg/dL three months or more beyond HPE.
- Moderate or severe refractory growth failure that does not respond to intensive nutritional support
- Complications of portal hypertension (that cannot be managed with other measures).
- Repeated variceal bleeding.
- Refractory ascites that compromises respiratory, bowel or renal function.
- Hepatopulmonary syndrome.
- Portopulmonary hypertension.
- Progressive liver dysfunction.
- Intractable pruritus.
- Refractory coagulopathy

Preemptive transplant is not recommended.[26] After liver transplant the prognosis is generally good with survival rates of 70% to 80% at both 5 and 10 years.

BA patients can receive whole or segmental deceased donor grafts, as well as segments from living donor. Postoperative outcomes appear to be less favorable in patients with BASM and poor nutrition, so vigorous nutritional support is essential in the pre and postoperative care of these patients.[2,3,27-29]

COMPLICATIONS

Post-operative complications include:

Cholangitis

The formation of a Roux-en-Y loop results in a bacterial stasis and colonization that predisposes to ascending cholangitis. The incidence is between 40-90%. In order to reduce the risk of cholangitis surgeons have tried surgical maneuvers (intussuscepted ileocecal conduit, omental wrap of the porta hepatis, anti-refluxing jejunal loop valve and stoma of the proximal limb of the Roux loop), none of these have proved useful. [30] Patients with an unsuccessful HPE (without bile drainage) have a low risk for ascending cholangitis.

Children with cholangitis present with fever without a clear source of infection, jaundice or acholic stools, elevation of liver enzymes and other laboratory abnormalities. Treatment should be early and aggressive with broad-spectrum intravenous antibiotics and good cover against gram-negative bacteria. Because the gravity of cholangitis most clinicians prescribe prophylactic antibiotics for at least one year after HPE, either trimethoprim-sulfamethoxazole (4 mg/kg/day trimethoprim and 20 mg/kg/day sulfamethoxazole) or neomycin (25 mg/kg/day divided four times daily) appear to be equally effective in decreasing the incidence of cholangitis.[2,3]

Recurrent cholangitis may predict the need for liver transplantation and can lead to progressive cirrhosis, however, one episode of cholangitis does not predict early transplantation.[1-3,31]

Portal Hypertension

Due to liver fibrosis and biliary cirrhosis induced by chronic hepatobiliary inflammation the portal venous pressure is high in most of infants with BA. Liver fibrosis is a time-dependent feature, so it correlates with age at HPE and bilirubin level. Portal hypertension can trigger variceal bleed, ascites and end-stage liver failure. In a registry study of 163 children with BA in North America who had not undergone liver transplantation (average age 9.2 years) 50% had portal hypertension, among those, 53% had history of variceal bleeding, 17% had ascites, and 34% had reduced hepatic synthetic function (prothrombin time >15 seconds or albumin <3g/dL). Recurrent variceal bleeding and refractory ascites are indications for liver transplantation.[3,31,32]

Variceal Bleeding

About 2 to 3 years after Kasai HPE 50-60% of children develop esophageal varices and out of these approximately 30% will bleed. Regarding this, is recommended that every child with BA undergo endoscopic surveillance. Those with active bleed require sclerotherapy or banding. After first variceal bleed, sclerotherapy and band ligation is instituted on a repeat basis with the ultimate goal of complete variceal obliteration, primary prophylaxis of esophageal varices is not indicated except in extenuating circumstances (i.e. The child is not reasonable proximity to emergency care).[1,2]

Ascites

Usually secondary to portal hypertension, hypoalbuminemia and hyponatremia. If ascites is severe enough to compromise respiratory function, it is treated with paracentesis followed by chronic administration of diuretics, beta blockers, salt and/or water dietary restriction.

Intrahepatic Cysts

Lakes or biliary cysts can cause recurrent episodes of cholangitis, in these cases prolong use of broad-spectrum antibiotics is recommended, if fail to respond liver transplantation is required.

Hepato-Pulmonary Syndrome

Syndrome characterized by cyanosis, dyspnea, hypoxia and digital clubbing. Is thought that the diffuse intrapulmonary shunting occurs due to gut-derived vasoactive compounds that have bypassed the sinusoidal inactivation. Liver transplantation is usually required to reverse the process.[33]

Malignancy

Rare cases of hepatocellular carcinoma or cholangiocarcinoma have been reported in cirrhotic livers after HPE.

PROGNOSIS

Main determinants of a satisfactory outcome after HPE:[34]

- Younger age at intervention: Better outcomes have been documented when HPE is performed before 60 days of age because liver fibrosis is a time-dependent factor, however, the age at Kasai HPE and surgical outcomes do not have a linear relationship.
- Syndromic type of BA: Children with BASM have less respond to Kasai surgery and poorer overall outcome with higher risk of death. CMV IgM(+) BA is the variety with poorest outcome and higher risk of death.

- Achievement of postoperative bile drainage: Satisfactory bile flow and clearance post-HPE has shown to have a better survival outcome with native liver. Serum AST 1-year post-HPE is a strong predictive factor for liver dysfunction, however, serum bilirubin post HPE is the most predictive biomarker of outcome and is predictive of native liver survival. In a prospective cohort, those patients with total bilirubin <2mg/dL three months after HPE, two-year survival without transplantation was 86%, while those with ≥ 2 mg/dL three months after HPE, survival without transplantation was only 20%.[1,32]
- The expertise of the surgeon and care center at which the procedure is performed. Although controversial, it appears that a center that performs at least five Kasai H
- HPE per year has better success rate, as measured by 5- or 10-year long-term survival with native liver.[32]

The complementary and sequential approach of HPE and liver transplantation affords long-term survival, with upward 90% of BA patients surviving into adulthood. Five-year survival is better in patients undergoing transplant after two years of age (97.1%) compared with those transplanted less than two years of age (93.8%).[2]

Overall survival with native liver ranges from 30% to 55% at 5 years, 30% to 40% at 10 years, and 20% to 40% at 20 years.[29]

FOLLOW-UP

Check TSB 30 days and 3-6 months after HPE. Routinely monitor growth and liver function tests, monitor yearly for esophageal varices with endoscopy.[3]

PREVENTION AND SCREENING

Some countries with a high incidence of BA have introduced a screening method. Either TSB or they issue the mother color-coded stool cards and ask to compare it with their infant´s stool. To help parents distinguish between normal and acholic stools, printed stool color cards (sensitivity 76.5%, specificity 99.9%), WebPages and a free Smartphone application (PoopMD for iOS and Android) have been developed. Recognition of pale stool prompts further investigation and early referral.[2,35,36]

CONCLUSIONS

BA is a rare birth defect; it remains a surgical disease with good outcomes with HPE. Although genetic factors and associations have been identified, BA seems to have multifactorial etiologies, which remain unclear. Early study of obstructive jaundice is the key to perform HPE before 90 days of life and to diagnosing BA, in those cases who do not have successful drainage after operation, liver transplant remain the only option. Universal screening using stool color cards and other methods may improve age at diagnosis, treatment and outcomes for children with BA. The 10-year survival after HPE has improved over time. This reflects an improvement in the technique of HPE, advances in liver transplantation, immunosuppressive strategies and medications. The centralization of specialty centers has also contributed to the overall improved effect of standardized patient care.[37]

CONFLICTS OF INTEREST

None.

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