Biliary Atresia

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Introduction

Biliary atresia (BA) is a severe hepatobiliary disorder in infancy characterized by a progressive, inflammatory process of extrahepatic as well as intrahepatic bile ducts leading to fibrosis and obliteration of the biliary tracts [1, 2]. It is the most common cause of severe chronic liver disease in infants and the most frequent indication for pediatric liver transplantation. BA is uniformly fatal within 3 years if left untreated.

Reported incidence of BA varies in different geographic areas (Table 13.1). The annual incidences (per 10,000 live births) was 0.5–0.6 in Europe (UK, France, and the Netherlands) [3–5]; 0.65–0.74 in the southeast region of the USA [6, 7]; 1.06 in Hawaii [8]; 0.7 in Victoria, Australia [9]; 0.74–0.8 in Japan [10]; 1.5–1.7 in Taiwan [11]; and 3.2 in French Polynesia [12]. The highest incidence of BA occurs in Asians. BA is more common in females compared to males at a ratio of 1.5:1.

The abnormal anatomy in affected patients varies markedly and is classified into three types according to the level of extrahepatic obstruction of the biliary tree. Type I (about 5 %) and type II (about 2 %) refer to the segmental obliteration of common bile duct and common hepatic duct, respectively, and type III (>90 %) involves the whole extrahepatic biliary tree to the level of porta hepatis (Fig. 13.1) [13].

Two clinical phenotypes of BA have also been described. Most patients with "classical" BA (about 80–90 %) have no associated extrahepatic congenital anomalies. About 10–20 % of infants with BA have variable combinations of associated extrahepatic congenital abnormalities, including situs inversus, asplenia/polysplenia, preduodenal portal vein, absence of inferior vena cava, intestinal malrotation, and cardiac malformations. These patients are classified as having biliary

Table 13.1 Reported incidence of biliary atresia in different geographic regions over the world

Region	Incidence of BA/10,000 live births	Author
Europe		
UK		
British islets	0.6	McKiernan et al. [3]
France	0.51	Chardot et al. [4]
Netherlands	0.5	Houwen et al. [5]
USA		
Texas	0.65	Strickland et al. [6]
Atlanta	0.74	Yoon et al. [7]
Hawaii	1.06	Shim et al. [8]
Victoria, Australia	0.7	Danks et al. [9]
Asia		
Japan	0.74–0.8	Chiba et al. [10]
Taiwan	1.5	Lin et al. [11]
French Polynesia	3.2	Vic et al. [12]

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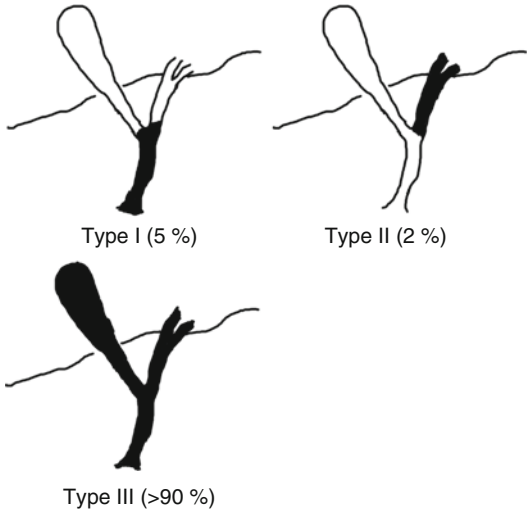

Fig. 13.1 Macroscopic types of biliary atresia. Type I and type II refer to the segmental obliteration of common bile duct and common hepatic duct, and type III involves the whole biliary tree to the level of porta hepatis

atresia splenic malformation (BASM) [14, 15]. BASM occurs more frequently in females and is less common in the Far East and Asia. The two types of BA appear to be different in pathogenesis and timing of disease onset. "Classical" BA is also named "perinatal," "sporadic," or "acquired" form. BASM syndrome is also called the "fetal," "embryonic," or "congenital" form.

Etiology and Pathogenesis of Biliary Atresia

The etiology of BA remains unclear. One hypothesis is that an acquired inflammatory disease of the bile ducts with subsequent damage to segments of the biliary tree results in obliteration of the extrahepatic bile duct and abnormal intrahepatic ducts [1, 2]. Viral infection may trigger an immune response with a continuing inflammatory process targeted at extrahepatic bile ducts. Three agents including cytomegalovirus (CMV), reovirus, and rotavirus have been extensively studied in animal models and in patients with BA [16–19]. Reovirus can induce intrahepatic cholangitis and extrahepatic duct dilatation but without the obstruction of extrahepatic bile duct when inoculated into newborn mice [20]. Inoculation of rhesus rotavirus in newborn mice triggers an inflammatory obstruction of extrahepatic bile ducts with features similar to those found in BA [21]. However, the identification of viruses in children with BA in different studies has been inconsistent [22–24].

In BA infants, the inflammatory response in the liver is periductal infiltration of mononuclear cells (T lymphocytes and macrophage) and amplification of HLA-DR expression on vascular and biliary epithelium, with increased expression of cytokines and receptors relevant to activated mononuclear cells [25]. In liver tissues from infants with BA, increased activation of interferon-γ, osteopontin, tumor necrosis factor-α, and other inflammatory mediators were found [26, 27]. A recent study found that liver T-cell response to CMV exists in the majority of BA patients at diagnosis and deficiency of T regulatory cells may decrease inhibition of inflammation and autoreactivity, potentially allowing for exaggerated bile duct injury [28]. In the rotavirus-induced newborn mouse model of biliary atresia, both immune and possible autoimmune mechanisms appear to mediate bile duct injury, and apoptosis of biliary epithelial cells is induced through the synergistic role of IFN-γ and TNF-α [29, 30].

Situs abnormalities in the congenital form of BA suggest that laterality gene may be related [31]. Mutations in the inversin gene have been found in experimental mice; however, such an association has not been found in the congenital form of human BA [32]. Recent studies have also revealed overexpression of five imprinted genes in children with the embryonic form compared with perinatal form of BA [33]—the significance has yet to be elucidated.

Clinical Features

BA typically occurs in normal birth weight infants who are discharged uneventfully from the newborn nursery. These infants may or may not have a history of physiologic jaundice, but cholestatic jaundice is usually detected by 2 weeks of age, and pale stool, icteric sclera, dark urine, and mild hepatomegaly are usually observed between 2 and 6

weeks of age. At this time, laboratory examinations show conjugated hyperbilirubinemia (direct bilirubin around 2–7 mg/dL and total bilirubin around 5–12 mg/dL), mildly elevated alanine aminotransferase (ALT) (around 80–200 IU/L), and elevated alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) levels. Splenomegaly secondary to portal hypertension may be evident, but commonly develops at a later time. Ascites or cutaneous signs of chronic liver diseases are rare at this early stage. Thereafter, the patients become progressively ill with failure to thrive and signs of chronic liver disease and eventually with chronic liver failure and death by the age of 2–3 years unless surgical intervention (hepatic portoenterostomy) is performed and successful [34, 35].

Screening for Cholestatic Infants and Early Identification of Biliary Atresia

Newborn infants have high incidence of jaundice. If the jaundice persists beyond 2 weeks of age, it is called prolonged jaundice. Prolonged jaundice in the neonates is usually unconjugated hyperbilirubinemia (such as breast-feeding-related jaundice) and resolves. Prolonged jaundice with conjugated hyperbilirubinemia (cholestasis) occurs in a wide variety of disease entities during the neonatal period. Extrahepatic cholestasis such as biliary atresia and intrahepatic cholestasis such as neonatal hepatitis syndrome are among the most common causes of neonatal cholestasis. Early detection of BA can prevent additional liver damage due to the delay of referral and surgical treatment [35]. Thus, the primary goal in the evaluation of prolonged neonatal jaundice should be early detection of BA.

Screening tests make it possible to detect neonatal cholestasis at an early age. Our previous study revealed that 95.2 % of infants with BA had persistently clay-colored or light yellowish stools [36]. Careful observation of stool color may help to identify infants who need additional assessment to exclude the possibility of BA. Screening of newborns for BA using stool color cards was initiated by Matsui et al. in the early 1990s [37, 38]. They designed an infant stool color card to increase the efficacy of the 1-month check in identifying BA in Japan. Based on this experience, we designed our own stool color card in Taiwan, which initially imprints pictures of 6 different stool colors from infants to educate the caretakers and the medical personnel. We then conducted a nationwide screening program using this stool color card from January 2004 [39]. In this program, parents were asked to observe the stool color of their infants in accordance with this card and notified their doctors of the results at 1 month of age (30 days) during routine health check. An increased proportion of infants undergoing portoenterostomy before 60 days of age (74.3 % in 2005, compared with historical rates of 23 % from 1976 to 1989 and 47 % from 1976 to 2000) was found [39–41]. The sensitivity and specificity of stool color card screening tests in Taiwan were 72–97 % and 99.9 %, respectively [40]. The results confirmed that stool color card is a simple, efficient, and applicable mass screening method for the early diagnosis of BA and has effectively increased the rate of hepatic portoenterostomy before 60 days of age (Fig. 13.2). The screening and register process using stool color card are shown in Table 13.2.

Other screening methods, such as conjugated bilirubin measured in liquid neonatal screening bloods between 6 and 10 days of age, have been proved to be a sensitive and specific marker of neonatal liver disease including BA in the UK [42] (Table 13.2). Measurement of total and direct bilirubin in infants with jaundice at 3 weeks of age was also recommended by the American Academy of Pediatrics (AAP) [43]. If conjugated hyperbilirubinemia was found within the first weeks of life, infants with cholestasis would be identified at earlier age. Fractionation of the total bilirubin to identify the conjugated bilirubin level should therefore be done in any infantile jaundice beyond 2 weeks of age.

Diagnosis

For infants with prolonged jaundice, the initial steps should include (1) confirmation that the conjugated bilirubin is >2 mg/dL or >20 %

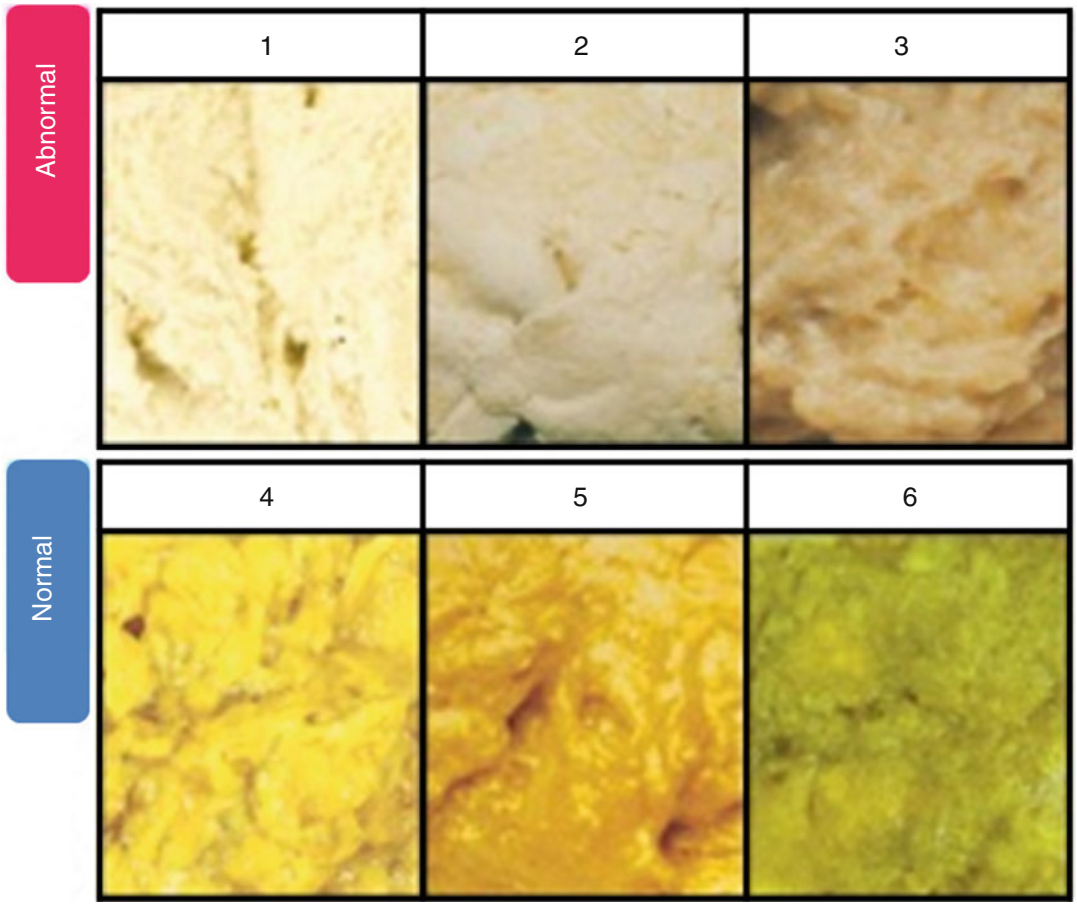

Fig. 13.2 The stool color card used in Taiwan for screening of neonatal cholestasis including biliary atresia. Images *1–3* represent acholic stool, whereas images *4–6* represent normal pigmented infant stool color

of the total bilirubin level; (2) identification of potentially treatable causes such as sepsis, hypothyroidism, or metabolic conditions; and (3) differentiating intrahepatic cholestasis from biliary atresia or obstructive condition such as choledochal cyst.

The evaluation of neonatal cholestasis usually begins with conventional liver function profile (total and direct bilirubin, alkaline phosphatase, *r*-glutamyl transpeptidase (GGT), aspartate aminotransferase, alanine aminotransferase, albumin, and prothrombin time). This evaluation alone provides very limited value in differentiating BA from other causes of neonatal cholestasis, although serum GGT is usually higher in BA, especially when correlated with age [2].

Because history taking, physical examination, and basic laboratory examinations do not reliably distinguish BA from other causes of cholestasis, the initial work-up should also include (1) serum bile acid determination; (2) cultures of blood and urine; (3) TORCH (toxoplasmosis, other agents [such as syphilis, varicella, parvovirus B19], rubella, CMV, and HSV); (4) alpha-1-antitrypsin phenotype; (5) metabolic screening including measurement of urine and serum amino acids and urinary organic acids with urinary succinyl acetone (to exclude tyrosinemia) and testing of urine-reducing substances (to exclude galactosemia); (6) thyroxine- and thyroid-stimulating hormone and cortisol level; (7) sweat chloride testing (needed only in prevalent regions of cystic fibrosis); (8) ultrasonography; (9) hepatobiliary

Table 13.2 Methods of screening and early identification of neonatal cholestasis including biliary atresia

Stool color card program
Stool color card is attached to child health booklet
Parents observe the infant stool color and report to registry center, if it is abnormal (acholic); or notify doctors the results at 1-month health check
Medical staffs check the number of the picture chosen by the parents and collect the card at 1-month health check. If the number is 4–6 (normal), the card is collected and sent to registry center. If the number is 1–3 (abnormal), the card is forwarded to register center by fax or telephone within 24 h
Registry center mail the screening results to collaborating hospitals and clinics, and contact the parents to provide related information
Newborn testing for conjugated bilirubin level
Conjugated bilirubin is measured in liquid neonatal screening bloods collected during routine newborn home visits by public health nurses between 6 and 10 days after delivery
Pediatricians and primary care providers are educated about the role of routine testing for conjugated bilirubin level measurement during the assessment of jaundiced infants more than 1-week old. A finding that the fraction of direct bilirubin more than 20 % of the total bilirubin concentrations prompts further evaluation and referral

Table 13.3 NTUH 3 days protocol for cholestasis in early infancy

Examinations on day 1
Biochemistry (3 cc): AST, ALT, ALP, *r*-GT, Alb, Ca, P
Alpha-fetoprotein
Bile acid (3–5 cc)[a]
PT/PTT (2.7 cc)
CBC/DC+ blood smear
Check results of newborn screen
Urine tests: urinalysis, bacterial culture, CMV isolation, urine GC mass
Examinations on day 2
Abdominal sonography[a]
Serum tandem mass and amino acid
Serology for CMV (IgM), CMV (IgG), rubella (IgM), herpes, and toxoplasma antibody (5 cc)
VDRL(2 cc)
Alpha-1-antitrypsin (1 cc)[b]
Urine tandem mass and bile acid[b]
Examinations on day 3
Liver biopsy[b]
Hepatobiliary scanning (MRCP), if BA or choledochocyst highly suspected

[a]Fasting at least 4 h, may consider IV fluid supplement if fasting time more than 4 h required. Ursodeoxycholic acid should be withdrawn for at least 3 days before bile acid measurement

[b]Optional, according to the decision of attending gastroenterologist, especially when patient is older than 60 days of age

scintigraphy and/or magnetic resonance cholangiopancreatography (MRCP); and (10) liver biopsy. The first seven tests largely exclude infectious and metabolic causes of cholestasis, leaving anatomic abnormalities and idiopathic neonatal hepatitis to be identified and differentiated. These evaluations should be completed within a few days. A "3-day protocol" is currently the author's work-up in differentiating BA from other causes of neonatal cholestasis to facilitate timely diagnosis and surgical intervention for BA (Table 13.3). It is also very helpful to accelerate the process of differential diagnosis for infants with cholestasis.

Real-time ultrasonography can demonstrate biliary anatomy and is useful in identifying anatomic abnormalities other than BA, such as choledochal cyst, that might be responsible for the obstructive cholestasis. Ultrasonography may detect associated anomalies such as polysplenia, vascular malformations, and situs inversus. In BA, the gall bladder is usually small or absent. Failure to find the gall bladder after an adequate fast is highly suggestive of biliary atresia. Changes in gall bladder size on sonography after a milk feeding occur in nonobstructive causes of neonatal cholestasis because of patency of the common hepatic and common bile duct. Gall bladder contractility is unlikely in patients with BA, as the biliary tree is obstructed [44]. Additionally, a fibrotic remnant of extrahepatic bile duct is echogenic on sonography and may be noted in the porta hepatis in BA. This finding has been termed "triangular cord sign" (seen as an area of increased echogenicity anterior to the bifurcation of the portal vein or a linear cord of echogenicity along the right portal vein) with a reported sensitivity up to 73 % [45, 46] (Table 13.4).

Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid derivatives is also used to differentiate BA from nonobstructive causes of cholestasis. In BA, prompt uptake of tracer by the hepatic parenchyma but no excretion into bowel is observed. Although administration of

Table 13.4 Diagnostic tests to differentiate biliary atresia from other causes of cholestasis

Procedure	Result significance	Comments
Ultrasound	The following findings are suggestive of BA: 1. After 4–6 h fasting, an absent gall bladder or one with irregular outline 2. Triangular cord sign 3. No changes of gall bladder size after feeding	Accuracy is operator-dependent; help to exclude anatomic structural abnormalities such as choledochocysts or vascular anomalies consistent with polysplenia syndrome but not diagnostic for BA
Radionuclide scanning	Excretion of tracer into bowel in 24 h in general excludes BA. Slow excretion of tracers (>24 h) may be seen in early phase of BA	High sensitivity but lower specificity because other cholestatic disease also impair excretion of the tracers. Disadvantage is time delay and cost
Percutaneous liver biopsy	Bile ductular proliferation with bile plugs is highly suggestive of BA. Absence of this finding does not exclude BA	Help to exclude other diseases like paucity of intrahepatic bile ducts, metabolic and storage disease, neonatal giant cell hepatitis, infection, and neonatal sclerosing cholangitis. Biopsies should be read by an experienced pathologist. Liver biopsy done early in the course of BA may be indistinguishable from hepatitis
MRCP	Visible extrahepatic bile ducts and gall bladder in general exclude BA	Requires deep sedation or general anesthesia and higher cost. High accuracy reported in a few studies

MRCP magnetic resonance cholangiopancreatography

phenobarbital (5 mg/kg/day) for 5 days before the scan can enhance biliary excretion of the isotope, it may delay performance of the test and hence the time of diagnosis. Hepatobiliary scintigraphy is a sensitive but not specific test for BA [47]. MRCP in the diagnosis of neonatal hepatitis is based on demonstration of well-visualized extrahepatic bile duct, thereby excluding biliary atresia as a diagnosis [48].

Liver histological study can accurately predict extrahepatic biliary obstruction in more than 90 % of cases. Liver histology in BA patients shows varying degrees of portal tract fibrosis, ductal proliferation, and cholestasis with bile plugs. However, typical histological features for BA may be absent if liver biopsy was taken early in the development of BA [49] or if performed too late, after the hepatic damage is severe.

If the abovementioned procedures fail to rule out BA, surgical exploration is indicated. When BA is suspected, intraoperative cholangiogram remains the gold standard for diagnosis. The definite diagnosis is made when the atretic biliary tree is clearly observed at laparotomy or when operative cholangiography fails to show a patent biliary tree. When BA is identified hepatic portoenterostomy (HPE) should be undertaken. Final diagnosis of BA is confirmed by histological examination of excised biliary remnants.

Management for Biliary Atresia

Surgical Management for Biliary Atresia

Kasai hepatic portoenterostomy is currently the standard surgical procedure for BA worldwide. This operation involves excision of the extrahepatic bile ducts and anastomosis of a limb of jejunum to the liver. Distal duodenum is anastomosed to the jejuna limb to create Roux-en-Y. After the Kasai operation, restoration of adequate bile flow, defined by the disappearance of jaundice with achievement of a normal bilirubin level within 3 months of the procedure, is the earliest indicators of success. If bile flow is not rapidly established in the first months of life, progressive obliteration and cirrhosis will ensue.

Although late Kasai portoenterostomy is frequently unsuccessful in reestablishing bile flow, the rate of success is greatest if done early, at younger than 2 months of age [50]. A retrospective cohort study in the USA showed that patients with a good outcome (survival with the native

liver and a bilirubin <2.0 mg/dL at 24 months of age) had Kasai operation at an earlier average age (57 days) than those with a poor outcome (64 days), but the difference was not statistically significant [51]. Other studies showed that the increasing age at Kasai operation may be accompanied by the progression of liver fibrosis and the obliteration of the biliary tree [52]. A study in Japan showed a significant survival advantage for BA infants operated on before 30 days of age and a significant disadvantage for those operated on later than 90 days of age [53]. Consistent results were also observed in studies from Canada and France [54]. Other factors affecting the outcome after HPE are size and patency of residual bile ducts at the transected porta hepatis and the experience of the center [3, 55].

The benefit of Kasai operation is the restoration of bile flow which may prevent or delay the onset of cirrhosis and sustain growth. Unsuccessful HPE usually requires liver transplantation and is the most common indication for liver transplantation in children.

Postoperative Complications and Management

Cholangitis

Cholangitis is a common complication in BA after Kasai operation and has an adverse effect on bile flow. Clinical features of cholangitis include recurrence or aggravation of jaundice, abdominal pain, fever, and elevated C-reactive proteins, serum bilirubin, and aminotransferase levels. Most episodes of cholangitis develop in the first 2 years after Kasai operation and usually respond well to intravenous antibiotics such as ceftriaxone continued for 14 days if pathogen was identified by septic work-up before antibiotic therapy [56, 57]. The most commonly identified pathogen is *E. coli*, occurring in 50 % of first and second episode. Recurrent cholangitis may be due to intrahepatic cystic dilatations (bile lakes) which can be detected by ultrasonography [58]. Multiple bile lakes with repeated cholangitis may indicate a worse prognosis. Prevention of cholangitis is an important issue because of reduced survival rate in patients with repeated episodes of cholangitis [57]. The authors use trimethoprim-sulfamethoxazole (4 mg/kg/day) or neomycin (25 mg/kg/day) as prophylactic antibiotics after the first episode of cholangitis [56]. This appears to be effective against the recurrence of cholangitis after the Kasai operation and benefit short-term survival.

Portal Hypertension

Patients with BA usually have a persistent inflammation of intrahepatic biliary tree, which continues in some infants who have initial restoration of bile flow after HPE [59]. This suggests that biliary atresia is a dynamic process involving an entire hepatobiliary system. Mild portal hypertension may have been present at the time of initial surgery. Progressive fibrosis and liver dysfunction occur in about 70 % of children whose jaundice resolves after the Kasai procedure. This may account for the ultimate development of portal hypertension with or without esophageal varices [60]. Although variceal bleeding sometimes resolves spontaneously, rebleeding is a common problem without therapy. Variceal bleeding without spontaneous resolution is frequently controlled by octreotide and/or endoscopic therapy. Esophageal variceal ligation or injection of sclerosing agents is the treatment of choice. While ligation is as effective as sclerotherapy with less complications, the size of the device limits its introduction in small children and infants. Other interventions such as transjugular intrahepatic portosystemic shunts (TIPS) can be used to bridge to transplantation, when octreotide and variceal ligation/sclerotherapy are insufficient to control variceal bleeding. Although splenic shunt or beta-blockers have been used as other options, supportive data are limited, and therefore their routine use is not widely accepted as standard of care for children with BA.

Ascites

Ascites is a poor prognostic sign in BA patients with chronic liver disease. Treatment includes low-sodium diet (1–2 mEq/kg/day) with or without fluid restriction, diuretics (spironolactone, hydrochlorothiazide, or furosemide),

and paracentesis. Refractory ascites may be effectively treated with TIPS, but is an indication for liver transplantation.

Other Complications

Hepatopulmonary syndrome may occur when incompletely metabolized vasoactive substances cause abnormal shunting in the pulmonary vascular bed and lead to hypoxia [55]. Malignancy such as hepatocellular carcinoma has been found in native liver [61].

Adjuvant Medical Therapy

Steroid has been used for improving bile flow after hepatic portoenterostomy, but its effect remains controversial [2]. Steroid has anti-inflammatory and immunomodulatory effects on continuous inflammation of intrahepatic bile ducts after operation. These are thought to increase bile salt-independent bile flow. Beneficial effect has been shown in some retrospective studies [62, 63], but was not confirmed in a recent prospective, randomized, placebo-controlled study [64].

Oral ursodeoxycholic acid (10–20 mg/kg/day) has also been used for stimulating bile flow and its possible liver protective effect after operation. Its beneficial effect was shown in a recent prospective study using withdrawal and reintroduction method [65].

Nutrition Support

Nutrition is one of the most important problems after Kasai operation, particularly in the first 2 years of life. Chronic liver inflammation and cholestasis lead to increased caloric requirement and malabsorption, resulting in growth failure in the first year of life. Energy expenditure is increased in chronic liver disease [66]. Malabsorption in BA infants is due to inadequate bile flow and passive congestion of intestine because of portal hypertension. Therefore, children with BA may need estimated caloric needs up to 150 % that of a normal healthy young child [66]. However, excess free water intake may worsen ascites. Enteral nutrition, such as nasogastric tube feeding, may be instituted to meet their caloric needs in those with poor intake, before the development of malnutrition. With diminished bile flow, BA children usually have inadequate digestion and absorption of dietary long-chain triglycerides and fat-soluble vitamins. Breast milk, infant formula, and food can be supplemented with medium-chain triglyceride (MCT) oil at least in the first year of life. MCT is directly absorbed into the portal venous system and do not require emulsification by bile acids in the duodenum. A formula such as Portagen, Pregestimil, or Alfare, in which major component of the fat is MCT, improves weight gain in cholestatic infants.

Deficiencies of vitamins A, D, E, and K should be suspected if cholestasis lasts 6 months or longer. All BA children should receive fat-soluble vitamins, and their vitamin levels should be monitored frequently to adjust supplement appropriately. Fat-soluble vitamin supplementation should include vitamin A (5,000–15,000 IU/day), vitamin D (alfacalcidol) (50 ng/kg/day), water-miscible form of vitamin E (TPGS, d-α tocopheryl polyethylene glycol-1000 succinate) (25 IU/kg/day), and vitamin K (2.5–5 mg/day) [67]. Poor nutrition and growth while awaiting liver transplantation is associated with increased risk of death and graft failure after liver transplantation [68].

Liver Transplantation

BA is the most common indication for liver transplantation (LT) in children. LT is reserved for those with failed Kasai operation. There are other indications relevant to advanced stage of liver disease, including progressive cholestasis, growth failure, refractory ascites, intractable pruritus, deteriorating coagulopathy, repeated gastrointestinal bleeding due to portal hypertension, repeated episodes of cholangitis, and multiple bile lakes or bilomas in the liver [69]. LT should be delayed when BA children are relatively healthy to allow for maximal growth. This is because of favorable techniques to perform surgery, more possibility to receive all necessary

vaccines, and fewer complications such as lower risk of posttransplant lymphoproliferative disease (PTLD) in older children [70]. However, LT is often required within 2 years of life for patients with poor bile drainage after Kasai operation and still be required beyond the age of 5 because of deteriorating portal hypertension and intractable biliary tract infection [41]. Many children in the world die from the complications of BA while waiting for liver transplantation due to the shortage of liver donation.

Biliary atresia patients can receive whole or split cadaveric livers or segments from living donors. Living-related liver transplantation has been frequently used in countries with shortage of cadaveric liver donation and was reported to have a high 5-year survival rate (98 %) in the recipients [71]. For pediatric patients with BA who underwent primary liver transplantation, the 1-year patient and liver-graft survival rates were 92.1 and 83.6 %, respectively, and 10-year patient and actuarial graft survival were 86 and 73 %, respectively [72]. The advances of surgical technique and immunosuppressive therapies have markedly improved outcomes in BA patients following liver transplantation. However, infants or children who undergo liver transplantation still face long-term immunosuppressive therapy, which can affect life quality, renal function, and life expectancy [73].

Prognosis After Kasai Operation

In Europe and North America, the native liver survival rate after HPE is ranging from 25 to 60 % during a period of 2–10 years' follow-up [3, 4, 7]. A Canadian study showed the native liver survival rates of 46 % at 2 years, 36 % at 4 years, and 26 % at 10 years and the overall survival rate of 77 % after HPE [54]. In a report from Japan, the overall rate of clearance of jaundice after Kasai procedure is 60 %, the 10-year survival rate with the native liver is 50 %, and the overall 10-year survival rate (with or without transplantation) is more than 90 % [53]. Another report from Japan found that more than 80 % of those who have had a successful Kasai procedure survive longer than 10 years with their native liver with good quality of life [74].

More recently, the stool color card screening program for BA in Taiwan enhances early Kasai operation (age at Kasai operation <60 days) (66 % vs. 49 %), increases the jaundice-free rate with native liver at 3 months postsurgery (57 % vs. 32 %), and markedly improves the 5-year jaundice-free survival with native liver (64 % vs. 27 %) and the 5-year overall survival rate (89 % vs. 56 %) of BA patients screened by stool color card, as compared to BA patients born before the stool card screening program [75].

Conclusion

While the improved medical and surgical management and liver transplantation have prolonged survival, further investigation on the etiology and pathogenesis of BA will hopefully provide effective therapy to intervene the development and progression of the disease in the future.

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