Surgical Treatment of Biliary Tract Malformations in Newborns

79

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Contents

Abstract

The most common biliary malformations in newborn requiring early surgical treatment are represented by biliary atresia (BA), congenital bile duct dilatation (CBDD), and solitary liver cysts (SLCs). **Biliary atresia** (BA) is the first

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cause of neonatal cholestatic jaundice. The origin of BA still remains unclear; if untreated, it usually leads to exitus within the first 2 years of life; therefore, early diagnosis is mandatory to plan a timely surgery, preferably earlier than 70 days. The Kasai operation can achieve good results in about a half of cases, but even children successfully treated suffered from liver failure, so the majority of these patients need liver transplantation later in life. Actually, the sequential use of Kasai operation and liver transplantation has dramatically increased the survival rate of patients with BA. **Congenital bile duct dilatation** is a relatively rare malformation of the pancreatobiliary system; the etiology remains essentially unclear. The cyst usually occurs with asymptomatic jaundice that may be mild and intermittent or progressive due to complete biliary obstruction. The surgical procedure of choice is total excision. **Solitary liver cyst** is a benign lesion with unknown etiology. They are often asymptomatic and identified incidentally or antenatally in the third trimester. Intervention is required among children who are symptomatic for a mass effect. On the basis of recent studies and fortieth experience of our Center, we summarize the current status of diagnosis and therapy of these biliary tract malformations.

79.1 Salient Points

- Biliary atresia (BA) is a progressive necroinflammatory obliterative cholangiopathy involving the intra- and extrahepatic bile ducts.
- Ultrasound plays a critical role in the diagnosis of BA; atretic gallbladder, "triangular cord" thickness (>3.4 mm), and hepatic subcapsular flow appear to be the most significant predictors of BA.
- The current surgical management of BA provides Kasai portoenterostomy (KPE) in neonatal period, which aims to restore bile flow, and later liver transplantation, when the KPE has failed.
- Congenital bile duct dilatation (CBDD) rarely occurs in the first months of life and is primarily a disease of older infants; it presents with jaundice, abdominal pain, and a right hypochondrial mass.
- Solitary liver cyst is a benign lesion; total excision or enucleation depends on the anatomical type of lesion.

79.2 Biliary Atresia

79.2.1 Introduction

Biliary atresia (BA) is a progressive necroinflammatory obliterative cholangiopathy involving the intra- and extrahepatic bile ducts. The disease arises during the first days of life and usually evolves into obliteration of extrahepatic bile ducts with interruption of bile flow, resulting in cholestasis and progressive liver damage. If untreated, BA leads to cirrhosis, hepatic failure, and exitus within the first 2 years of life. Early diagnosis is mandatory to plan a timely surgery, preferably within 70 days of life.

Although the surgical treatment can achieve a good relief of cholestasis in about a half of cases, even children successfully treated show the consequences of liver deterioration, namely, hepatic fibrosis or cirrhosis with portal hypertension, so the majority of BA patients need liver replacement later in life (Caccia et al. 2004). Actually, BA is still the most common indication for pediatric liver transplantation worldwide, with dramatic increase of the survival rate of BA patients during the last few decades (Lee et al. 2013).

BA is the most common cause of cholestatic jaundice in newborn, and its prevalence is about 1:10.000–15.000 live births, meaning approximately 700 newborns affected every year in Europe, with a small female preponderance. Incidence of BA is highest in Asian and Pacific populations and familial cases have been reported (Chardot 2006).

Obliteration of bile ducts can involve the extrahepatic biliary tree, partially or completely, and the types of BA are classified according to the most proximal level of obstruction: **type I** involves just the common bile duct; **type II** also involves the cystic and the hepatic ducts; and **type**

III, present in more than 95% of cases, involves all extrahepatic biliary ducts and represent the most severe form of BA.

Two forms of BA have been identified, which can be defined clinically: (**1**) **isolated BA** (~**90**%), representing the largest but not homogeneous group, because of variation in time presentation, degree of cholangiopathy, and obliteration of biliary tree, and (**2**) **syndromic BA and associated malformations** (~**10**%), with female predominance. This may be further divided into a *BA splenic malformation* (*BASM*) *syndrome*, with congenital anomalies such as polysplenia, asplenia, cardiac or intra-abdominal defects (situs inversus, preduodenal portal vein, absence of retrohepatic inferior vena cava, intestinal malrotation), and *BA with random malformations*, as esophageal or jejunal atresia (Davenport 2012).

79.2.2 Etiology and Pathogenesis

The etiology of BA still remains largely unknown. Some cases seem to be related to abnormal morphogenesis of bile ducts occurring early in pregnancy with cholestasis from birth (*embryonic or fetal BA*, 35% of cases), while many cases appear to arise from later damage to normally developing bile ducts, with onset of symptoms at the age of about 4 weeks (*perinatal or acquired BA*, 65% of cases) (Baumann and Ure 2012).

Several epidemiologic studies have pointed toward a potential association between viral infection and BA. An association with some virus infections (CMV, RSV, EBV, and HPV) has been reported, while no association with hepatitis A, B, and C viruses has been found (Chardot 2006). The viruses most commonly implicated are *Reoviridae* and *Rotaviridae*. In human neonates, the association of reovirus type III and BA has been suggested, but not confirmed otherwise. The role of rotavirus type C in the etiology of BA in humans remains still controversial, because of the few published studies and their incomplete accuracy. Thus, currently there are no studies that can definitively prove a viral etiology of BA (Saito et al. 2015).

The role of immune-mediate mechanism in the pathogenesis of BA has been based by the assumption that the initial damage of biliary epithelium is followed by the activation of immune cells and the release of proinflammatory cytokines that perpetuate the injury up to biliary destruction, which is followed by collagen deposition to produce biliary fibrosis (Besso and Bezerra 2011; Srivastava 2011; Sira et al. 2015).

The progressive liver damage, the presence of lymphocytes in the liver of patients with BA, and the association with HLA-B12 have suggested an autoimmune persistent injury against the biliary epithelium (Alvarez 2013).

Defect in fetal circulation and exposure to environmental toxins has also been proposed. Recently, the role of gene ADP ribosylation factor-6 (ARF6) in defective bile duct formation, leading to BA, has been postulated (Ningappa et al. 2015).

Therefore, BA does not seem to be a single disease, but a phenotype, resulting from a number of different and separate etiologies.

79.2.3 Clinical Aspects

The clinical signs are jaundice persisting beyond 14 days of age, alcoholic stools, dark urine, and hepatomegaly. The liver gradually increases in size and consistency along with aging. Splenomegaly also follows hepatomegaly, suggesting portal hypertension. The general condition of the newborn is usually good with adequate weight growth; mild jaundice is often missed and the diagnosis is established later. When the patients are untreated, the majority of them will die of hepatic failure, esophageal variceal bleeding, and infections (Caccia et al. 2004).

79.2.4 Diagnosis

Antenatal diagnosis of BA remains exceptional. Since early diagnosis appears essential for successful surgical treatment, neonatal jaundice lasting more than 14 days should be investigated for BA. There are many causes of pathological jaundice in the neonatal period, and the most likely to be confused with BA are neonatal hepatitis syndrome and interlobular biliary hypoplasia. When

newborn shows jaundice, alcoholic stools, dark urine, and hepatomegaly with hardening in consistence, BA should be strongly suspected (Caccia et al. 2004).

Biochemical liver function tests show increased total bilirubin (TB) with predominance of direct bilirubin (DB) more than 50% and high levels of γGT, ALT, and AST (more than two to three times of normal values). BA is very strongly suspected with the presence of TB greater than 4.5 mg/dL, DB more than 80% of TB, and γGT greater than 500 UI/L (Caccia et al. 2004).

Ultrasound (US) plays a critical role in the diagnosis of BA. Some US findings have been described as useful indicators of BA, as abnormal gallbladder morphology, "triangular cord" sign, visualization of the extrahepatic bile duct, diameter of the hepatic artery, and presence of hepatic subcapsular flow. Between these, atretic gallbladder, "triangular cord" thickness (>3.4 mm), and, more recently, hepatic subcapsular flow appear to be the most significant predictors of BA (Lee et al. 2015; El-Guindi et al. 2013). US also is helpful in the assessment of splenomegaly or associated anomalies, such as polysplenia.

Hepatobiliary scintigraphy (e.g., Tc-99m DISIDA) shows a failure of excretion of the radioisotope into the intestine, but has relatively poor discrimination with severe neonatal cholestasis from whatever cause. Endoscopic retrograde cholangiopancreatography (ERCP) (Shanmugam et al. 2009) and MR cholangiography play a limited role in the diagnosis of BA because they may be performed in selected skilled centers only.

The definitive diagnosis is based on detection of fibrosing obstruction of the extrahepatic bile ducts during exploratory laparotomy, cholangiography, and liver biopsy (Caccia et al. 2004). The main histological features suggestive of BA are ductular proliferation, portal fibrosis, and absence of sinusoidal fibrosis (Russo et al. 2011). Overall, the predictive value of liver biopsy for BA was 91%. Recently, some countries have adopted a simple population screening program for BA. In Taiwan, it has allowed to shorten the time to surgery, with the median age at intervention being <50 days, representing the best result achieved anywhere (Hsiao et al. 2008).

79.2.5 Therapy and Treatment

The current surgical management of BA provides Kasai portoenterostomy (KPE) in neonatal period, which aims to restore bile flow, and later liver transplantation, when the KPE has failed (Chardot 2006).

The KPE provides a careful dissection to locate patent bile duct remnants in the porta hepatis with the restoration of biliary flow by a 45 cm Roux-en-Y loop anastomosis to the hepatic hilum. Alternative laparoscopic approach was reported since 2002 (Estevez et al. 2002), but results are certainly not better and rarely comparable to standard open approach nowadays (Ure et al. 2011).

The best surgical results after KPE are obtained in children operated within 60 days of life, with early satisfactory biliary drainage in at least 70% of cases (Nio et al. 2010), resulting in increased pigmentation of stools and progressive resolution of jaundice. The outcome of surgery may be improved by early postoperative adjuvant high-dose steroid therapy (oral prednisolone, IV methylprednisolone, or hydrocortisone), which does have a significant benefit in reduction of postoperative bilirubin and clearance of jaundice (Tyraskis and Davenport 2015). However, the effect of steroids may be limited or inhibited by an increasing fibrosis and onset of cirrhosis, due to delayed diagnosis and surgery.

Thus, the age at treatment is one of the most important factors determining surgical outcome that can be influenced by reduced effectiveness of adjuvant therapy and postoperative complications.

The most common complications following the KPE are cholangitis and portal hypertension. Rare complications include hepatopulmonary syndrome, pulmonary hypertension, intrahepatic biliary cavities, and malignancy (Chardot 2006).

Cholangitis occurs particularly in the first weeks or months after operation in 33–60% of cases and clinically is characterized by fever, vomiting, jaundice, choluria, and alcoholic stools; treatment requires IV antibiotics and corticosteroids. Portal hypertension occurs in at least two-thirds of children after KPE, with the appearance of varices in the esophagus, stomach, and Roux loop. Treatment requires variceal sclerotherapy or band ligation. Factors shown to predict

outcome after KPE include age at operation, experience of the surgeon, anatomical type of BA, and relapse of cholangitis (Caccia et al. 2004; Lee et al. 2013; Chardot 2006; Davenport 2012).

79.2.6 Prognosis

Overall, KPE results in clearance of jaundice from 38% to 62% of patients in various series (Davenport 2012), with a mean native liver survival rate of 53% at 5 years (Shinkai et al. 2009), while the other patients develop progressive hepatic failure that leads to liver transplantation (Caccia et al. 2004; Lee et al. 2013).

The choice of sequential treatment by KPE and late liver transplantation is supported by the following reasons: firstly, performing liver transplantation in all children with BA would deprive some of these of the possibility to live with their own liver, while the long-term results of liver transplantation and prolonged immunosuppression are not entirely known; secondly, performing transplantation on all children with BA will dramatically increase the need of pediatric liver grafts at this time when the shortage of organs is as yet an unsolved problem; and lastly, liver transplantation at older age reduces the period of immunosuppressive therapy (Caccia et al. 2004).

The overall prognosis of BA has improved since the early days of pediatric liver transplantation. Currently, about 90% of children with BA, treated sequentially by KPE and liver transplantation, have an acceptable quality of life (Lee et al. 2013).

79.3 Congenital Bile Duct Dilatation

79.3.1 Introduction

Congenital bile duct dilatation (CBDD) is a relatively rare malformation of the pancreatobiliary system with an incidence of 1:100,000–200,000 and a female predominance (3:1 to 4:1). For unknown reasons, it is most common in Asian countries, especially in Japan.

A maternally inherited condition, such as an X-linked dominant trait, has been suggested recently. Several cases of familial recurrence have been reported (Iwasaki et al. 2008).

In 1977, Todani classifies CBDD in five types: **type I**, cystic dilatation of the common bile duct (80% of cases); **type II**, *diverticulum* of the common bile duct (10%); **type III**, choledochocele (4%); **type IV** (11%), (**a**) intra-extrahepatic bile duct dilatation and (**b**) plurisegmental common bile duct dilatation; and **type V**, isolated intrahepatic bile duct dilatation (<1%).

79.3.2 Etiology and Pathogenesis

The etiology of CBDD remains speculative. In majority of patients, an anomalous pancreatobiliary duct junction with a long common channel involving the common bile duct and the main pancreatic duct is present and may be a responsible factor for CBDD, allowing reflux of activated pancreatic proenzymes into the biliary system and leading to duct wall destruction and dilatation. Distal common bile duct stenosis or obstruction may add to ductal dilatation. An autonomic dysfunction by diminished ganglion cells in the distal common bile duct causing partial obstruction and proximal dilatation has been suggested.

79.3.3 Pathology

Two histopathological types of CBDD that may be present concurrently or separately have been described: the "glandular" type, in which there are microscopic cavities in the mucosal layer with chronic inflammatory infiltrate, and the "fibrotic" type, in which the wall is composed mainly of fibrous tissue with interrupted elastic fibers, well-developed collagen fibers, and lower inflammation.

79.3.4 Clinical Aspects

Rarely, it occurs in the first months of life, and in fact it is primarily a disease of older infants and young children, because more than half percent of cases presents in the first decade of life. The

classic presentation of CBDD with jaundice, abdominal pain, and a right hypochondrial mass is seen only in one-third of children. Infants usually present with asymptomatic jaundice that may be mild and intermittent or progressive due to complete biliary obstruction. Late complications in cases with delayed or escaped diagnosis are represented by cholelithiasis, cirrhosis, portal hypertension, liver abscess, spontaneous rupture, and cholangiocarcinoma (Benjamin 2003).

79.3.5 Diagnosis

There are no specific laboratory tests, and the initial diagnosis is made by US. The findings of a dilated common bile duct with US are helpful for early diagnosis of CBDD. TC may show the cystic dilatation better than US; it does not however demonstrate ductal anatomy (Takaya et al. 2003). Because preoperative biliary duct imaging is essential, the diagnosis must be confirmed by the MRC, especially when dealing with the fusiform type (Fitoz et al. 2007). ERCP requires an experienced endoscopist and must be done in older infants or young children with caution, in order to avoid infection of the cyst or precipitate pancreatitis. In most cases, CBDD have been demonstrated antenatally by US.

79.3.6 Therapy and Treatment

In the past, internal drainage by cystoenterostomy or partial cyst excision was considered the preferred surgical treatment. Nevertheless, this procedure led to significant morbidity due to recurrent cholangitis, cholelitiasis, pancreatitis, and even cholangiocarcinoma.

Today, total excision of the CBDD with a Roux-en-Y hepaticojejunostomy and cholecystectomy is widely considered the treatment of choice. Before intervention, a cholangiography through the gallbladder is performed to demonstrate accurately the anatomy of the cyst and the pancreatobiliary ductal system.

When the ductal dilatation extends into the main hepatic ducts, after excision of involved ductal structures, polyductal Roux-en-Y jejunostomy must be performed. In case of choledococele which is located inaccessibly within the distal common bile duct, complete surgical excision is precluded. The approach should be transduodenally, and the presenting wall of choledococele is excised with marsupialization of choledococele into the duodenum.

The laparoscopic excision of CBDD is an alternative surgical approach whose first large pediatric series was published in 2004 (Li et al. 2004). This is technically feasible, safe, and effective with a comparable outcome to open procedure. Additional benefits are less postoperative pain with less pulmonary complications, a shortened period of ileus, and less adhesion formation (Aspelung et al. 2007). For these reasons, this procedure should be considered as a good alternative to standard surgical approaches; nevertheless, it is technically demanding and requires advanced skills (Liem et al. 2009).

More recently, it has been proposed to use the robotic surgery for surgical treatment of CBDD, considering that the three-dimensional vision, the high motion stability, and the scaling wound effect would be a greater benefit for the hepaticojejunostomy (Naitoh et al. 2015). However, the small series reported cannot show a definitive advantage of this technique at present.

79.3.7 Prognosis

Although the surgical management of CBDD is successful in 90% of cases, early complications can occur in 2.5–25% of patients and include biliary or pancreatic fistula, biloma, and cholangitis (Takeshita et al. 2011). Late complications occur in 25% of patients and are represented by cholangitis, delayed anastomotic stricture, intrahepatic calculi, and liver failure (Ohtsuka et al. 2015). Cholangiocarcinoma was rarely observed in patients with cysts removed in infancy, but the risk of carcinogenesis increases with age (Xiao-dong et al. 2014).

79.4 Congenital Solitary Liver Cyst

79.4.1 Introduction

Solitary liver cyst (SLC) is a benign lesion more common in females (2:1), and it can be classified as simple solitary liver cyst and solitary intrahepatic biliary cyst (Macedo 2013; Berg et al. 2002). Early report suggested that their incidence was 0.17% based on autopsy findings. The spectrum of potential pathologies causing congenital solitary liver cysts in children is wide (Rogers et al. 2007).

79.4.2 Etiology and Pathogenesis

The etiology of simple congenital cysts is unknown. They are generally thought to develop from aberrant bile ducts, which are obstructed from the main biliary system or as result of a vascular disruption during the fetal period (Berg et al. 2002).

79.4.3 Pathology

Simple cysts are typically unilocular, lined by a single layer of cuboidal or columnar epithelial cells, resembling biliary cells. The cystic layer can secrete fluid similar to serum and may be clear, brown, or, occasionally, bilious (Howard 2002). They rarely communicate with the biliary tree and are not considered premalignant. They may be completely intrahepatic, partially extrahepatic, or pedunculated. The presence of septa is usually regarded as a pointer to other pathologies and the need for further investigations (Rogers et al. 2007).

79.4.4 Clinical Aspects

Most solitary liver cysts are asymptomatic and identified incidentally or antenatally in the third trimester (Berg et al. 2002; Charlesworth et al. 2007). Simple cysts rarely cause symptoms unless become enlarged. Symptoms are usually vague, and in such cases pain, hepatomegaly, abdominal distension, feeding difficulties, respiratory distress, and duodenal obstruction have been reported (Shankar et al. 2000). Infection, hemorrhage, and spontaneous rupture are other rare complications.

79.4.5 Diagnosis

US is widely used for the diagnosis of SLC (Liang et al. 2005). US should demonstrate the cyst location, loculation, wall contour and characteristics, content, and associated pathology. In the differential diagnosis, TC and MRI should be able to show a mesenchymal hamartoma and rarely embryonal sarcoma as well as cystic teratoma (Charlesworth et al. 2007; Celebi et al. 2014). In selected cases, functional hepatic scintigraphy may be useful in distinguishing simple from choledochal cyst by the different radioisotope uptake (Rogers et al. 2007).

The differential diagnosis of upper quadrant abdominal cysts and masses includes hepatobiliary lesions such as liver cysts, parasitic cysts, benign tumors (mesenchymal hamartoma, cystadenoma), malignant tumors (sarcoma), choledochal cysts, and type I BA, other intra-abdominal cysts (ovarian, omental, mesenteric, adrenal, or renal cysts), and different conditions such as dilated bowel loops and duodenum and gallbladder duplications (Soyer et al. 2007).

79.4.6 Therapy and Treatment

Because of the scarcity of case series, the optimal management of simple hepatic cyst remains controversial. Most unilocular cysts do not require intervention postnatally, and conservative management of cysts smaller than 10 mm has been suggested. Intervention is required among children who are symptomatic for a mass effect or complications such as infection, hemorrhage, or rupture with peritonitis

(Charlesworth et al. 2007; Shankar et al. 2000; Liang et al. 2005; Celebi et al. 2014). Various treatment options, including percutaneous aspiration, percutaneous injection sclerotherapy, laparoscopic excision, or fenestration, have been reported as a possible alternative to open surgery (Celebi et al. 2014).

The total excision or enucleation seems to be the treatment of choice, but will depend on the anatomical type of lesion. If this is not possible, partial excision with deroofing of the cyst wall is recommended (Berg et al. 2002; Shankar et al. 2000; Celebi et al. 2014). During surgery, communication with the extrahepatic and intrahepatic biliary system has to be ruled out by cholangiography (Berg et al. 2002). In case of a biliary cyst, a Roux-en-Y cystoenterostomy or hepaticojejunostomy as described for CBDD is recommended (Howard 2002).

79.4.7 Prognosis

The postoperative course can be complicated by bile leakage, cholangitis, septicemia, and recurrence of the cyst (Berg et al. 2002; Rogers et al. 2007). Children who undergo incomplete excision must be followed up closely for recurrence (Celebi et al. 2014).

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