Congenital hepatobiliary defects: Medico-surgical Perspectives

Prof. Yogesh Kumar Sarin,
MS, DNB, MCh, MBA, FAMS
Head, Dept. of Pediatric Surgery
MAMC & assoc. LNH, New Delhi

Introduction

Intrahepatic bile ducts (IHBDs) develop from bipotential liver progenitor cells in contact with the mesenchyme of the portal vein and thus form the "ductal plates." The ductal plates are remodeled into mature tubular ducts. Lack of remodeling results in the persistence of periportal epithelial sleeves or "ductal plate malformation" (DPM). It has been proposed that virtually all congenital diseases of IHBDs represent examples of DPM at different levels of the biliary tree. Many of these diseases are characterized by dilatation of segments of IHBDs and variable degrees of fibrosis— the so-called 'fibrocystic diseases' of the liver. Some early, severe types of extrahepatic bile duct (EHBD) atresia are also characterized by DPM, a suggestion of a prenatal beginning of the disease. This brings us to a novel unifying concept of origin of most of the congenital hepatobiliary defects.

Congenital cystic lesions of intrahepatic bile ducts include five entities: congenital hepatic fibrosis (CHF), Caroli's disease, von Meyenburg complexes, simple cyst of the liver and polycystic liver disease. Congenital cystic lesions of extrahepatic bile ducts consist of choledochal cyst (CDC).

CHF and von Meyenburg complexes are secondary to ductal plate malformation affecting the smallest intrahepatic bile ducts. Cystic dilatations are of small size and only detected at histological examination of the liver. In congenital hepatic fibrosis, the main manifestations result from portal hypertension.

Caroli’s disease is secondary to ductal plate malformation affecting the largest intrahepatic bile ducts. Cystic dilatations are macroscopic and responsible for cholangitis and may lead to biliary stones and carcinoma which develop within cystic dilatations. Caroli's disease associated with congenital hepatic fibrosis is termed as Caroli’s syndrome.

Simple cyst of the liver and polycystic liver disease are characterized by cystic dilatations which, by contrast to the preceding entities, do not communicate with the rest of biliary tree.

In CHF and polycystic liver disease, renal abnormalities are frequently observed. They correspond to renal malformations associated with biliary malformations. In congenital hepatic fibrosis, renal lesions are characterized by ectatic collecting tubules which are present in two thirds of the cases and transmitted as an autosomal recessive trait. In polycystic liver disease,
renal lesions are characterized by polycystic disease which is present in half of the cases and transmitted as an autosomal dominant trait.

Congenital cystic lesions of extrahepatic bile ducts consist of CDC, which is secondary to pancreato-biliary ductal malunion (PBDMU). The major risk of CDC is the development of intracystic cancer, the prevention of which is total surgical resection of the cyst.

Besides these congenital hepato-biliary defects, inspissated bile syndrome (IBS) has been also briefly discussed. Though there may not be similar underlying defect, jaundice is a predominant feature here too.

Main content areas:

- Congenital hepatic fibrosis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Choledochal cyst
- Inspissated bile syndrome

**Congenital hepatic fibrosis (CHF)**

CHF is a rare autosomal recessive disease that primarily affects the hepatobiliary and renal systems. Progressive destructive cholangiopathy occurs leading to periportal fibrosis, secondary biliary strictures and portal hypertension. CHF has 4 different forms: portal hypertensive (most common), cholangitic, mixed, and latent. Associated splenomegaly with hypersplenism is common. CHF usually presents in adolescent or young adulthood, but onset of signs and symptoms can range from early childhood through mid-life.

Differential diagnoses include other ductal plate malformations (e.g., biliary cysts, Caroli Disease, choledochal cyst).

Diagnostic blood tests include deranged LFTs, and KFTs. If cholangitis is present, leucytosis is seen. If hypersplenism is present, leucopenia and thrombocytopenia are predominant. Imaging studies include abdominal ultrasonography, CT scan, IVP, splenoportography, angiography, transhepatic cholangiography, MRI and MRCP. Diagnostic and therapeutic upper G.I. endoscopy may be done for bleeding varices resulting from portal hypertension. Liver biopsy is diagnostic. A percutaneous liver biopsy may not be very useful. Ideally, a wedge liver biopsy should be taken through mini-laparotomy or laparoscopy. Histopathology of liver biopsy shows a widened portal tract with bands of fibrous tissue that separate areas of normal hepatic parenchyma. Lobular and portal inflammation is absent.
Medical therapy includes management of cholangitis with broad spectrum antibiotics. Other important aspect is management of portal hypertension and variceal bleed (pharmacotherapy, sclerotherapy, banding, TIPS, etc.)

Surgical therapy includes portosystemic shunt surgery. Different nonselective total portosystemic, nonselective partial portosystemic, or selective portosystemic shunts could be employed. Type of shunt is to carefully selected so that renal or hepatic transplantation remains a future option, with minimal limitations and complications. Liver transplantation indicated for recurrent cholangitis or failure to respond to various medical and surgical therapeutic modalities resulting in progressive hepatic dysfunction.

**Primary biliary cirrhosis (PBC)**

Primary biliary cirrhosis (PBC) is a chronic and progressive cholestatic disease of the liver due to autoimmune destruction of small and medium sized intrahepatic bile ducts. The underlying hypothesized etiologies include genetic and infective causes.

The inflammation impedes the flow of bile which ultimately leads to liver cirrhosis. It is usually associated with a variety of autoimmune-mediated diseases (e.g., autoimmune thyroiditis; keratoconjunctivitis sicca; scleroderma; CREST syndrome [calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia]).

Onset of PBC usually occurs in persons aged 30-60 years. However, patients as young as 17 years have been reported.

Differential diagnoses include other conditions with similar symptoms, such as autoimmune hepatitis or primary sclerosing cholangitis (PSC). Diagnostic blood tests include deranged LFTs and presence of certain antibodies such as AMA and ANA. Imaging studies like abdominal ultrasonography, CT scan, or MRI are important to exclude biliary obstruction. Diagnostic and therapeutic upper G.I. endoscopy may be done for bleeding varices resulting from portal hypertension. Liver Biopsy is diagnostic. Similar to CHF, a percutaneous liver biopsy may not be very useful. Ideally, a wedge liver biopsy should be taken through mini-laparotomy or laparoscopy. Histopathologic findings of PBC include inflammation of the bile ducts, characterized by intraepithelial lymphocytes, and periductal epitheloid granulomata.

Medical therapy includes choleretics (e.g., UDCA), immunosuppressants, antipruritics (e.g., antihistamines such as Hydroxyzine hydrochloride in the dose of 0.6 mg/kg/dose PO q6h), colestipol, Rifampin, dronabinol), bile acid sequestrants (e.g., cholestyramine), vitamins A, D, E, K supplementation, corticosteroids, methotrexate, cyclosporine, and colichicine.

Management of portal hypertension and variceal bleed (pharmacotherapy, sclerotherapy, banding, etc.) is indicated in many.

Liver transplantation is indicated for severe liver cirrhosis.
**Primary sclerosing cholangitis (PSC)**

Primary sclerosing cholangitis (PSC) is a chronic and progressive disease of the liver due to autoimmune inflammation and scarring of the larger bile ducts. The inflammation impedes the flow of bile to the gut, which can ultimately lead to liver cirrhosis and cholangio-carcinoma. Many have associated inflammatory bowel disease. It is uncommon in children; usual presentation is from 30 to 60 years. Lifetime risk of cholangiocarcinoma for PSC sufferers is 10-15%. Features of obstructive jaundice, liver cirrhosis and liver failure are present.

Differential diagnoses include primary biliary cirrhosis, drug-induced cholestasis, cholangiocarcinoma and HIV-associated cholangiopathy. LFT and liver histology are not diagnostic. ERCP or MRCP is diagnostic; typical “Beading” (both strictures and dilation) of the intra and extrahepatic ducts is seen. Autoantibodies such as p-ANCA are positive in most of the cases.

Medical therapy includes choleretics, vitamins A, D, E, K supplementation, bile acid sequestrants, antipruritics, and antibiotics. Immunosuppressants play a doubtful role. An interventional radiologist may help with endoscopic dilatation of predominant strictures of CBD with or without stenting.

Surgical drainage procedures (e.g., portoenterostomy, choledochoenterostomy) are insignificant in the management of primary sclerosing cholangitis. These procedures may provide palliation but do not alter the natural history of the disease because of the consistent involvement of the intrahepatic biliary tree. Surgical drainage procedures are associated with an increased risk of cholangitis postoperatively, and subsequent liver transplantation may become technically more difficult.

Orthotopic liver transplantation (OLT) has been proven successful in treating children with primary sclerosing cholangitis. Indications for liver transplantation include recurrent bacterial cholangitis, jaundice refractory to medical and endoscopic treatment, decompensated cirrhosis, complications of portal hypertension, progressive muscle wasting, and hepatic encephalopathy. Data from numerous liver transplant centers demonstrate excellent long-term patient and graft survival for patients with end-stage primary sclerosing cholangitis. Actuarial patient survival rates after OLT for primary sclerosing cholangitis at 1 and 5 years have been shown to be greater than and approximately equal to 90%, respectively.

These patients may also require proctocolectomy for associated inflammatory bowel disease.

**Caroli’s disease**
In Caroli disease, abnormalities of the bile duct occur at the level of the large intrahepatic ducts (i.e., left and right hepatic ducts, segmental ducts), resulting in dilatation and ectasia. Resulting biliary stasis may lead to cholelithiasis, cholangitis, and sepsis, as well as an increased risk of cholangiocarcinoma. In Caroli’s syndrome, Caroli’s disease coexists with congenital hepatic fibrosis and ARPKD. Patients with Caroli’s syndrome or Caroli’s disease have recurrent cholangitis and may also have complications of portal hypertension. Risk of cholangiocarcinoma is very high.

Differential diagnoses include cholelithiasis, CHF, PSC, cholangitis, polycystic liver disease, hepatic abscesses. Diagnostic blood tests include deranged LFTs and KFTs. If cholangitis is present, patient would have leukocytosis. If hypersplenism is present, leucopenia and thrombocytopenia may be present. Carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) are used to screen for cholangiocarcinoma. Imaging studies include abdominal ultrasonography, CT scan, IVP, splenoportography, angiography, transhepatic cholangiography, ERCP, MRI and MRCP. Liver biopsy reveals typical findings of ductal plate (DP) malformation, with ducts arranged in a circumferential pattern around the portal vein branches and with a variable degree of associated portal fibrosis.

Medical therapy includes choleretics, vitamins A, D, E, K supplementation, and broad-spectrum antibiotics. Interventional radiologist could perform therapeutic ERCP for stone extraction, sphincterotomy, or biliary stenting.

Surgical therapy could involve the following:

- Hepaticojejunostomy or external drainage for recurrent or refractory cholangitis and obstructing stones.
- Portosystemic shunting may be indicated in patients who have portal hypertension
- In cases of localized stasis, lobectomy can be curative and can also reduce the risk of cholangiocarcinoma.
- Liver transplantation may be indicated in severe cases of refractory or chronic cholangitis, liver failure, or malignant transformation.

**Choledochal cyst (CDC)**

Cystic dilatation of the extrahepatic bile ducts is known as choledochal cyst (CDC). It is more commonly encountered in Japan and Asia. Most of the classifications describe 5 anatomical types of CDC:

1. Type I- saccular or fusiform dilatation of EHBD
2. Type II- diverticulum of EHBD
3. Type III- choledochocele
4. Type IV- multiple cysts of the intra- or extrahepatic ducts (or both)
5. Type V- single or multiple intrahepatic cysts (Caroli’s disease)
Some authorities believe that choledochocele and Caroli’s disease should not be described under the heading CDC as the underlying etiology, management and prognosis are different, but others feel that these entities are part of the same continuum.

With the use of prenatal ultrasonography, an increasing number of CDCs have been reported in the fetus. The prenatal demonstration of a cystic structure inferior to the liver strongly suggests the diagnosis. Fetal development should be carefully monitored with serial ultrasonography after such a discovery. Most centers prefer to excise the cyst shortly after birth. A waiting period of a few weeks is necessary to stabilize the baby and allow for proper preoperative evaluation. Surgical excision in the neonatal period has been shown to be technically feasible and well tolerated by the patient.

Two distinct clinical groups of patients are recognized with regard to age at presentation. The first group is the infantile group consisting of babies younger than 1 year, with or without obvious hepatomegaly, with obstructive jaundice and acholic stools. This clinical picture is indistinguishable from that of biliary atresia in the absence of a palpable mass in the right side of the abdomen. However, the cystic mass can usually be detected either at clinical examination or on ultrasonography; this finding suggests a diagnosis of CDC. In infants with a prenatal diagnosis of CDC, jaundice often does not manifest until 1-3 weeks after birth.

In contrast, infants older than 1 year, with the so-called adult form of CDC, generally have one or more components of the classic triad: pain, jaundice, and a palpable mass. The entire triad is present in very few patients. Jaundice is intermittent and often associated with vague abdominal pain. The pain has been described as being similar to that of cholangitis or recurrent mild pancreatitis. Undiagnosed CDC can lead to choledocholithiasis, cirrhosis with portal hypertension, cyst rupture, or biliary carcinomas.

Laboratory studies that may be useful for the diagnosis and preoperative evaluation of a patient with a CDC include direct bilirubin, alkaline phosphatase, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and coagulation profiles.

Imaging studies are the cornerstone of diagnosis of CDCs. They serve not only to confirm the diagnosis but also to outline the anatomy of the anomaly in preparation for surgical intervention.

Ultrasonography is the best initial study. In neonates, it may be the only test needed. Ultrasonography can demonstrate changes in the bile ducts as well as in the liver. Endoscopic retrograde cholangiopancreatography (ERCP) remains an important diagnostic study. In expert hands, it can be performed with a high rate of success, even in small infants and small choledochoceles. Magnetic resonance cholangiopancreatography (MRCP) has largely replaced ERCP as the diagnostic test of choice for CDCs because it offers high resolution detailed images of relevant anatomy, is noninvasive, and does not suffer from complications such as post-procedure pancreatitis. MRCP detects most CDCs with high degrees of sensitivity and specificity, with the exception of small choledochoceles and minor ductal anomalies. CT scanning may also
be useful to delineate the cyst and its relationship to surrounding structures. In older patients, especially adults, CT scanning combined with cholangiography may be useful. Scintigraphy with technitium-99m diisopropyl iminodiacetic acid (DISIDA) may show complete obstruction of the distal bile duct without any drainage to the intestine.

Treatment of CDCs is surgical, except in type V multiple intrahepatic cysts, which can benefit from medical management for variable periods of time. In the past, operative aspiration and external drainage were used extensively because most patients were quite sick, and a simple quick procedure was convenient. These external drainage procedures of the biliary tree were unsuccessful because of numerous complications, including repeated cholangitis and biliary fistulae. Mortality rates were high. Today, in the setting of acute severe disease, percutaneous cholecystostomy drainage can be performed prior to the definitive procedure. This is safe and generally well tolerated; however, it is not necessary in most patients.

Internal drainage, either with cystoduodenostomy or cystojejunostomy with Roux-en-Y biliary reconstruction, was used in the past. These procedures left the cyst behind, and the free reflux of pancreatic enzymes into the cyst via the anomalous pancreaticobiliary junction resulted in a high incidence of calculi, recurrent cholangitis, anastomotic strictures, and carcinoma arising from the cyst. Two-thirds of the patients treated with either cystoduodenostomy or cystojejunostomy remained symptomatic, and a sizable numbers required repeat surgery at a later date. Recurrent cholangitis and chronic inflammation in the remaining cyst eventually produces metaplasia that leads to malignant transformation.

Total excision of the cyst in types I, II, and IV followed by reconstruction of the biliary tree with hepaticojejunostomy in a Roux-en-Y fashion has been widely accepted as the procedure of choice in treating CDCs. Others have performed hepaticoduodenostomy instead. Some authors have interposed a reversed segment of jejunum to prevent reflux.

Total excision of the cyst is possible in all infants and young children. In older patients with repeated cholangitis and marked pericystic inflammation, this disease may be best managed with resection of the anterolateral part of the cyst followed by an endocystic resection of the lining, leaving the back wall adjacent to the portal vein in place, as reported by Lilly in 1977. This technique also appears to be most useful in patients who have previously undergone cystoenterostomy and who require repeat surgery because of recurrent cholangitis. This technique makes the dissection less hazardous. Several groups have successfully performed laparoscopic-assisted and laparoscopic total cyst excision with Roux-en-Y hepatoenterostomy with complication rates comparable to those of the open procedure.

With regard to type II CDCs, a simple excision of the diverticulum with ductoplasty for reconstruction of the CBD is all that is required. Laparoscopic excision has been successfully performed in this rather rare disease.

With type III CDCs, the general approach is one of lateral duodenotomy with unroofing of the choledochoccele to drain the bile duct and pancreatic duct directly into the duodenum. The two ductal openings should be carefully examined to determine whether ductoplasty is required.

In patients with type IV CDCs with intrahepatic cysts (type IVa), each case is individually evaluated, and the principle of adequate bile drainage is taken into account. Excision of the
dilated extrahepatic bile ducts as far as the porta hepatis, with hepaticojejunostomy at the level of the hilum, may provide good biliary drainage and effective decompression of the intrahepatic cysts. If the intrahepatic cysts are localized in a small portion of the liver, partial hepatectomy may be required.

With regard to type V CDCs, patients with localized disease may benefit from a hepatic lobectomy. If the disease is diffuse, involving both lobes of the liver, treatment is palliative and liver transplantation may be required.

Any type of cyst is susceptible to malignancy, but the greatest prevalence is observed with types I, IV, and V. The risk of cancer is high (>20 times) compared with that of the healthy population. Factors thought to contribute to the development of malignancy include prolonged bile stasis and chronic inflammation of the cyst wall. Inflammatory and metaplastic changes increase with patient age, and they are frequently observed in association with carcinoma of the bile duct. The increased risk of biliary tract malignancy, even after surgery, warrants close surveillance in any case of CDC. Total cyst excision has not prevented the risk of malignancy in the remaining bile ducts. Malignancy can develop many years after excision of the cyst and can develop in areas of the biliary tree remote from the cyst such as the gallbladder and terminal common duct, which is left behind after excisional surgery.

Other postoperative complications include biliary stone formation, residual debris in the intrahepatic bile ducts and anastomotic strictures. Apart from technical errors, anastomotic strictures may be a progressive phenomenon after surgery. The diameter of an adequate anastomosis is usually reduced by 20-30% after a few weeks. Such a reduction in the anastomotic diameter may result from excessive devascularization of the duct during dissection. A wide anastomosis as far as the hepatic hilum may prevent anastomotic stricture. Residual debris is commonly observed in older patients. Debris left within the intrahepatic duct or pancreatic duct during cyst excision may be responsible for post-excisonal stone formation and pancreatitis. Dilatation of IHBDs usually regresses after cyst excision and hepaticojejunostomy in young patients. In older patients and adults, this dilatation tends to persist. Dilatation and residual debris may cause cholangitis and stone formation. Some authors recommend endoscopic examination of the duct during surgery to clean out all the debris.

**Inspissated Bile Syndrome (IBS)**

Inspissated Bile Syndrome (IBS) is partial or complete obstruction of the extrahepatic biliary system by impaction of thick bile or sludge in the distal CBD in neonatal period. Pathogenesis involves increase in viscosity or decrease in solubility of bile resulting from the following diseases or predisposing factors:
IBS may precede cholelithiasis

The most important differential diagnosis is biliary atresia. Imaging studies that would help. Ultrasonography may reveal proximal biliary dilatation with biliary sludge or stones. Radionuclide scans may show hepatic concentration of isotope without excretion in the intestine, but even hepatic excretion may be absent in severe form of IBS. ERCP though technically difficult in neonates, it has been reported in literature for both diagnostic as well as therapeutic purpose. Intraoperative cholangiogram is the gold standard for diagnosis.

IBS usually resolves spontaneously on treatment of underlying disease or predisposing factor. Mild forms of obstruction may be cleared by percutaneous transhepatic irrigation of bile ducts or retrograde irrigation during ERCP examination. Surgical therapy includes cholecystostomy and intraoperative cholangiography along with irrigation of CBD with saline; N-acetylcystine has been also used for the wash-out. Duodenotomy, sphincterotomy and removal of inspissated bile has been occasionally performed. Cholecystectomy, sphincteroplasty with or without T-tube drainage has been done in few cases.