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Clinical Update

Biliary Atresia

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Keywords
Biliary atresia
Jaundice

Abbreviations
BA- Biliary atresia
KPE-Kasai Portoenterostomy
GGT-Gammaglutamyl transferase
ICL - Intrahepatic cystic lesions
LT-Liver transplant

Abstract

Biliary atresia is a common cause of neonatal jaundice. This article reviews the recent literature on biliary atresia. Recently near-infrared fluorescence cholangiography (NIR-FCG) using indocyanine green fluorescence (ICG) has been employed during Kasai portoenterostomy (KPE) to identify bile flow from hilar ductules. Intrahepatic cystic lesion (ICL) is a newly recognized complication of KPE. Patients with ICL developing after six months of KPE tend to have better outcomes. Usually, ICL are preceded by episodes of cholangitis. Higher GGT levels before KPE is now identified as a risk factor of post-operative cholangitis.

INTRODUCTION

Biliary atresia (BA) is a neonatal disease which presents as progressive inflammatory obliteration of the extra-hepatic ducts. This condition is the most common cause of persistent direct hyperbilirubinemia during the first three months of life. Furthermore, it is also the most common indication for liver transplants in children.

BA affects 1 in 15,000 live births and patients are mostly females. Without treatment, BA may cause cirrhosis, liver failure, and death. Even though its exact cause remains unknown, some possible etiologies have been suggested. Among them, transplacentally acquired viral infections were found to have strong association. Up to 68% of the affected infants have serum antibodies against reovirus type-3. Additionally, some genetic mutations have been identified as potential causes of developmental anomalies. Cases of polysplenia, malrotation, situs inversus, pre-duodenal portal vein, and absent inferior vena cava are some examples of developmental malformations associated with BA.

BA can be classified according to the localization of the biliary obstruction. (Fig. 1) Biliary atresia type-I (5%) represents obliteration of the common bile duct. Type-II (2%) can be subdivided into IIa and IIb (according to the Kasai classification) and it signifies obliteration of the common hepatic duct. In type-IIa, the cystic duct and common bile duct remain patent; thus, atresia is limited to the common hepatic duct. In type-IIb the common hepatic duct, cystic and common bile duct are affected. Type 3 is the most common form (more than 90% of cases) in which ductal obliteration extends to common bile ducts, cystic

duct, and left and right main hepatic ducts at the level of the hepatic transverse fissure.

Among treatments for BA, Kasai portoenter-ostomy (KPE) and liver transplant are known as leading therapies. KPE may be regarded as a primary surgical approach, but liver transplant is ultimately required for most of the patients. Prognosis can be determined by the promptness of work-up and referral to surgery. Degree of liver fibrosis and ductal plate malformations have also been related to prognosis.[1-4]

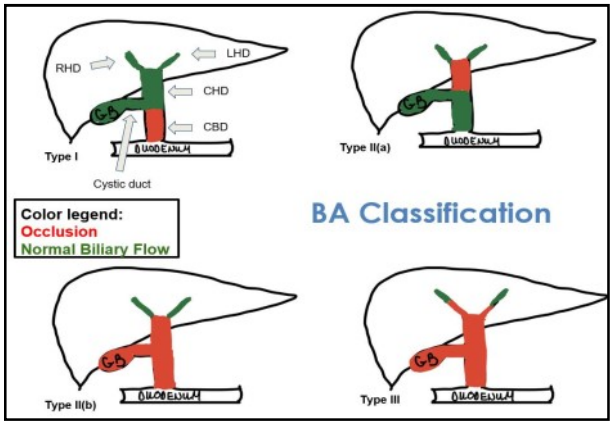

Fig 1. *Classifications of Biliary Atresia. RHD-right hepatic duct; LHD-left hepatic duct; CHD-common hepatic duct; CBD-common bile duct; GB-gallbladder. Orange colour - atretic segment, green colour-patent duct*

CLINICAL FEATURES

The clinical characteristics for BA include insidious jaundice by the second week of life. Upon evaluation, vital signs typically appear to be normal. Hence, despite apparently healthy look the infant may progressively develop acholic stools, choluria, and hepato-splenomegaly. Although not specific for this disease, weight loss and loss of appetite may be observed. Icterus may be noted at birth and it may persist for more than three weeks. Jaundice and acholic stools in an infant are specific but not sensitive indicators of BA. Cholestatic jaundice of infancy caused by neonatal hepatitis and BA are very similar. Thus, identification of BA may sometimes be complex and several differential diagnoses should be considered. (Box 1)

INVESTIGATIONS

Laboratory investigations used to identify BA include elevated total bilirubin level in serum with 50-80% of conjugated bilirubin. Lipoprotein-X levels are also elevated (> 300 mg/dl). Gamma-glutamyl-transpeptidase (GGT) level may be greater than 200 units/dl. Furthermore, lab tests utilized to exclude BA may include perinatal infectious panel (TORCH titers, hepatitis profile), indicators of metabolic disorders (α-1-antitrypsin levels) and markers of hemolysis (Coomb's test, reticulocyte count, peripheral smear).

GGT is an important enzyme measured in BA. It is an epithelial transferase associated to glutathione and its conjugate. Elevated levels of this enzyme indicate cholestatic diseases and it accurately differentiates BA from other cases of neonatal cholestasis. High GGT levels (> 500 IU/L) have been associated to lower rates of native liver survival. Yet, GGT levels are not routinely tested for and more research is needed to assess its prognostic worth.[5,6]

Box 1. Differential diagnosis of Biliary Atresia

- Physiologic Jaundice
- TORCH Infection
- Idiopathic Neonatal Hepatitis
- α-1-Antitrypsin Deficiency
- Alagille Syndrome
- Biliary Hypoplasia
- TPN-Induced Cholestasis.

IMAGING

In terms of imaging, ultrasound has been considered as the initial diagnostic tool of choice. It reveals triangular cord sign, absent gallbladders, and intra- or extra-hepatic bile ducts and liver parenchymal echogenicity. Demonstration of post-prandial contraction of the gall bladder eliminates the possibility of BA, further enhancing its diag-nostic relevance. Length and contractility of the gall bladder is also suggested to aid diagnosis.

However, several studies have concluded that the triangular cord sign is more useful sign rather than length and contractility of the gallbladder.[7]

Hepatobiliary scintigraphy, also known as Di-isopropyl imino-di-acetic acid (DISIDA) scans, is the diagnostic imaging of choice. These tests allow for evaluation of hepatic uptake and bilio-enteric excretion. The presence of this radio-isotope in the patient's gastrointestinal system excludes BA as a final diagnosis.

INVASIVE STUDIES

The three invasive studies are considered in the diagnosis of BA are percutaneous biopsy, laparoscopy, and mini-laparotomy. Firstly, the percutaneous biopsy was regarded as a safe procedure with a complication rate lower than 1%. It is deemed as a highly specific and sensitive method. Although these are not specific for BA, percutaneous biopsy allows evaluation for liver damage, ductular proliferation, bile plugs, giant cell transformations and fibrosis. (Fig. 2) However, immuno-histochemistry of the portal ducts may demonstrate the presence of the epithelial membrane antigen in large ducts, which is a specific feature of BA.[8-16] A histological scoring system has been developed at the Children's Hospital of Fundan University. This 21-point system demonstrated good diagnostic accuracy and consisted of eight features: liver fibrosis, portal ductal proliferation, bile plugs in portal ductules, cholestasis, hepatocellular changes inflammatory cells infiltration in portal region, extramedullary hematopoiesis, and ductal plate malformation.[20]

Nonetheless, it will be important to point out that preoperative biopsies are not indicated when laparoscopies are available. Biopsies are often considered as an unnecessary postponement delaying KPE.[17] On the other hand, combination of the laparoscopic technique along with additional tests may serve to diagnose BA accurately. This route spares the liver from trauma and provides a safer diagnostic protocol.

Alternatively, the mini-laparotomy is regarded as a final diagnostic alternative. It is majorly used for gall bladder cholangiograms and liver biopsies. Small hypoplastic ducts are associated to Alagille syndrome.[13] In BA, the gallbladder will be atrophic fibrous remnant or when present will be filled with white bile and no communication to biliary tree or distal extra-hepatic communication.

SURGICAL APPROACHES

Symptoms of BA are due to the inability of the system to excrete conjugated bile and inflammatory obliteration of bile ducts. Therefore, delaying without treatment may lead to an increase in fibrosis and a decrease in ductal size. These sequence results in a poorer prognosis. Conversely, surgery before sixty days may lead to improved prognosis and bile drainage in 75-80% of the cases. Thus, patients should be assessed early and referred promptly to surgery.

Preoperative management involves supplemental formula feed with medium chain triglycerides and fat soluble vitamins (A, E, D, and K). Parental education and support are recommended as well.

Operative management for KPE involves administration of intravenous fluids and prophylactic antibiotics. Surgeon's expertise is also crucial for proper technique during the procedure. In a given case, identification of severe cirrhosis should call for cessation of KPE and the patient should be referred for liver transplantation. The steps for KPE include beginning with a mini-laparotomy to rule out all other differential diagnoses. When BA is confirmed, the incision is extended and KPE is performed. Some studies have pointed out the importance of KPE as a temporizing procedure of future liver transplant surgery. Using a low subcostal incision well below the costal margin is essential for incorporation during a future liver transplant.[14] Moreover, this procedure consists of removing the obliterated extra-hepatic biliary system and making a jejunal conduit for bile drainage. The proximal jejunum is

attached to the jejunal conduit through a Roux-en-Y anastomosis. Extensive dissection of the duodenum and right colon should always be avoided and usage of a long jejunal loop for conduit reconstruction is recommended.[18-23]

Although feasible, a laparoscopic approach to KPE is shown to be unfavorable when compared to postulated advantages of laparoscopy.[4] Recently near-infrared fluorescence cholangiography (NIR-FCG) using indocyanine green fluorescence (ICG) has been employed during KPE. This technique facilitates observation of hilar micro-bile ducts and provides real-time visualization of bile flow during KPE. When compared to control groups, without NIR-FCG groups showed higher rate of postoperative normalization of hyperbilirubinemia.[22]

Post-operative management of KPE requires monitoring of liver function, bile flow, cholangitis and portal hypertension. Prevention of further complications must remain a top priority; thus, nutritional and familial support should always be available. Early and recurrent cholangitis lowers survival chances.[10] Cholangitis should be treated aggressively with antibiotics. Higher GGT levels before KPE is a risk factor for post-operative cholangitis. Occurrence of intrahepatic cystic lesions (ICL) is another potential complication post-KPE. Patients with ICL developing after six months of KPE tend to have better outcomes. Usually, ICL are preceded by episodes of cholangitis. Clinical symptoms for ICL may include fever, jaundice, leukocytosis, and acholic stools. Solitary cysts are amenable to percutaneous drainage. Portal hypertension may manifest as esophageal varices, hypersplenism, and ascites. Sudden cessation of bile flow, malabsorption, and pruritus are other complications of KPE.

When KPE fails, a liver transplant (LT) is needed for most patients. Total bilirubin levels greater than 2 mg/dl and albumin levels lower than 3.5 g/dl at three months of KPE are predictive of the necessity of LT. In fact, BA is the most common cause for pediatric LT. KPE remains as the initial surgical treatment choice for BA but is only considered a temporary solution. Minimal supra-colic dissections during KPE reduce post-LT morbidity and mortality. Bowel perforations following LT in BA are unfavorable. All in all, BA patients have excellent long-term survival chances.[18]

conventional surgery. Laparoscopic KPE has not been associated with fewer liver adhesions and it should be avoided in BA. However, the procedure still poses some advantages such as a faster recovery time, less postoperative pain, and reduced incisional morbidities. Future studies should provide sufficient data to support these

CONCLUSION

Although relatively rare, BA remains as the most common cause of end-stage liver disease and LT. Persistent cholestasis in newborns must be assessed with urgency. In this sense, KPE should be offered to infants before their sixty days of life. One-third of BA patients become long-term survivors with KPE. LT is indispensable for patients with failed KPE, liver failure or late referral to surgery. Some common indications for LT include bilirubin levels above 10 mg%, low albumin, weight loss, and uncontrolled ascites.

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