From the Symposium President

Dear Participants,

Biliary atresia is one of the most common liber transplant indications in pediatric patients. It is a complex disease that requires a multidisciplinary approach. Nutrition indices, complications of cirrhosis and portal hypertension, infections, and the extrahepatic organ systems should be closely monitored.

In the symposium, all aspects of patients with biliary atresia were discussed. In our opinion publication of the topics that were discussed during the symposium in our journal will contribute to the scientific armamentarium of our readers.

The president of the Symposium

Prof. Sezai Yilmaz, MD, FACS

Inonu University

Director of Liver Transplant Institute

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Symposium program

22 December 2023

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Sevgi Tasolar

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17.10-17.30 Liver Transplantation for Biliary Atresia

17.40 CLOSING REMARKS

Historical Overview of Biliary Atresia

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Abstract

The last half century has been accompanied by significant advances in the diagnosis and treatment of infants with biliary atresia (BA). Kasai portoenterostomy and liver transplantation have changed the poor prognosis of infants with biliary atresia. In this article, historical developments regarding the diagnosis and treatment of BA were mentioned.

Key words: Biliary atresia, Kasai portoenterostomy, liver transplantation

BA is a serious neonatal disease that occurs with occlusion of the intra or extrahepatic bile ducts. The first reference to BA comes from John Burns of the University of Glasgow in 1817.[1] Burns pointed out that jaundice in infancies with BA is an important disease and that the danger is great, especially if it occurs immediately after birth. He also emphasized that the absence of bile in the stool may mean the absence of the extrahepatic bile duct and the disease may be in an incurable state. The first review on this subject was written by John Thompson in 1892.[2] In this study, the author reviewed 50 cases collected from the literature, 1 of which was his own. He described the symptoms, pathology and natural course of the disease. According to Thompson, 16% of these cases could be corrected surgically. This idea was on a theoretical basis, and no surgical procedures were performed on patients with BA. In his article written in 1916, Holmes focused mostly on BA that could or could not be corrected surgically, but he did not mention any surgical procedure.[3] He examined 120 cases collected from the literature (1 of which was his own). He stressed about the diseases caused by fat malabsorption and problems in the digestion of various foods in these patients. However, until those years, no surgical correction of BA had been reported. Cases of BA corrected surgically were first reported by Ladd in 1928. This information was obtained from Ladd's article in 1935.[4] He reported the first successful reconstruction of correctable BA, reporting good results with surgery in the first 4 months in 8 of 11 infants. Gross emphasized in 1953 that BA was the most common cause of obstructive jaundice in infants.[5] Most of these were of a nature that could not be corrected surgically. For many years, no serious progress has been made in the surgical treatment of BA. This general frustration led to numerous surgical maneuvers to restore bile flow, but these were unsuccessful. In those years, congenital atresia of the bile ducts constituted the darkest part of pediatric surgery.

Professor Morio Kasai is a pediatric surgeon who trained in surgery and pathology in Los Angeles in the 1950s. In BA according to Kasai, between 2-12 months after birth, there was a decreased pseudoductular proliferation in the portal tract and progressive destruction of intralobular bile ducts (Hering's ducts). There were fibrous residues of atretic bile ducts in the porta hepatis. He mentioned that there may be continuities between the ductal plate of the porta hepatis and the intrahepatic biliary system. In this case, if a portoenterostomy was performed, the progression of the disease could be stopped. Even the presence of bile pigments in the stool of 30% of infants with BA was an indication that the duct obliteration was not complete. In 1968, Kasai reported that he achieved "operative relief" with portoenterostomy in infants diagnosed with non-correctable BA, with his 10-year experience.[6] After Kasai's article, "hepatic portoenterostomy" was considered the treatment of choice for BA. With increased experience, it has become accepted that early diagnosis and timely operations are essential for successful restoration of bile flow. However, successful long-term results were still very rare.[7]

The presentation of liver transplantation as a treatment option by Starzl and his colleagues in 1963 opened a new horizon in the treatment of infants with BA.[8] The current surgical strategy for BA is initially Kasai portoenterostomy (first 2 months), then, if necessary, liver transplantation.

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Etiopathogenesis in Biliary Atresia

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Abstract

Biliary atresia (BA) is a progressive, idiopathic, fibro-obliterative disease of the intra and/or extrahepatic biliary tree that presents with biliary obstruction, particularly in the neonatal period. The general incidence of this condition is approximately 1 in 10,000 to 20,000 live births. Biliary atresia is the most common indication for liver transplantation in children. It is observed more frequently in girls and non-white children. Low birth weight term babies (<2500 g) have a higher risk of developing biliary atresia compared to normal birth weight term babies. Familial transmission and occurrence in twins are rare. The cause of biliary atresia is currently unknown. The etiopathogenesis is thought to be influenced by various factors, including genetics, immunology, viral infections, toxicology, environment, and vascular causes.

Definition

Biliary atresia (BA) is a progressive, idiopathic, fibro-obliterative disease of the intra and/or extrahepatic biliary tree that presents with biliary obstruction, particularly in the neonatal period.[1]

History

Dr. John Burns from Glasgow University first mentioned it as 'an incurable condition of the biliary apparatus' in a textbook published in 1817.[2] In 1891, John Thomson, an Edinburgh physician, published a case report and review defining congenital obliteration of the bile ducts.[3]

Embryogenesis

The biliary system primarily develops during the first trimester. The extrahepatic bile duct is the first visible structure in the embryo. It arises from an outgrowth of the foregut endoderm, specifically the liver bud, beginning at about day 20 of gestation. By about day 45, it is essentially complete, with a funnel-shaped proximal segment in close contact with the gallbladder, lumen, and liver outline. The cholangiocytes within it appear to originate from the foregut endoderm. [4]

Epidemiology

The general incidence of this condition is approximately 1 in 10,000 to 20,000 live births. Biliary atresia is the most common indication for liver transplantation in children.[5]

It is observed more frequently in girls and non-white children. Low birth weight term babies (<2500 g) have a higher risk of developing biliary atresia compared to normal birth weight term babies. Familial transmission and occurrence in twins are rare.[6]

Classification

Babies with biliary atresia (BA) are classified into three categories.[7]

1. Biliary atresia without any other anomaly or malformation:

This group is also known as perinatal biliary atresia, which occurs in 70 to 85 percent of infants with BA. These infants are usually born healthy but develop jaundice within the first two months of life, and their stools become increasingly pale.

2. Biliary atresia associated with malformations of laterality:

This pattern is also known as biliary atresia splenic malformation (BASM) or 'embryonic' biliary atresia. It occurs in 10 to 15 per cent of infants with BA. Laterality abnormalities include situs inversus, asplenia or polysplenia, malrotation of the interrupted inferior vena cava and cardiac abnormalities. Data suggest that children with BASM have worse outcomes than children with perinatal BA, possibly because of the associated cardiac anomalies.

3. Biliary atresia in combination with other congenital malformations:

It accounts for 5-10% of BA cases. Associated congenital malformations include choledochal cyst, intestinal atresia, anal atresia, renal anomalies and cardiac malformations.

The classification of biliary atresia according to the site of involvement is shown in Figure 1.[6]

Biliary atresia is also divided into 2 types, correctable and uncorrectable. Correctable is the condition in which the proximal common hepatic duct is open, which accounts for 10-15% of cases and allows primary anastomosis of EHBDs to the bowel, whereas uncorrectable is the condition in which the common hepatic duct is not open.[6]

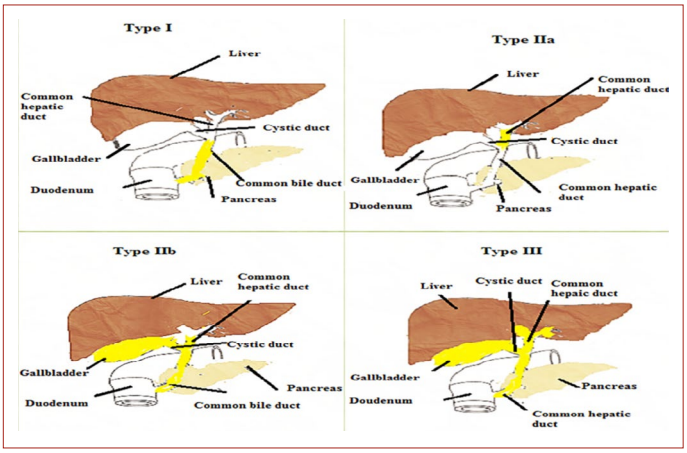

Figure 1. Classification of biliary atresia according to the site of involvement (yellow areas).

Etiopathogenesis

The cause of biliary atresia is currently unknown. However, it is believed to be associated with genetic defects in the formation of ductal plaque and bile ducts, or intrauterine ductal inflammation caused by viral or autoimmune factors. Although the exact trigger is uncertain, evidence suggests that biliary atresia begins in utero.[8]

Genetic Factors

BA is caused by mutations in the Jag1 gene, which plays an immunoregulatory role by suppressing the production of inflammatory cytokines such as IL-8.[9]

Some patients with sporadic BASM have been found to have mutations in the CFC1 gene, which is thought to act as a cofactor in the pathways determining the left-right axis. However, CFC1 mutations may predispose to BASM but are not sufficient to cause the disease.[10]

There is a contradiction about the relationship between HLA and BA. Some authors support this relationship,[3] while others do not.[11]

A new theory proposes that somatic mutations occurring after zygote formation affect only a subset of cells, leading to different phenotypes depending on the timing of the mutation. An earlier occurrence may result in de novo dominant disease, while later mutations can cause whole-body mosaicism or be limited to specific tissues. This concept also applies to BA phenotypes. The success rate of Kasai portoenterostomy (KPE) may be attributed to the rate of mosaicism in various regions of the liver.[12]

Imminological Damage

Initial studies published in the 1990s identified abnormal expression of ICAM-1 and, less frequently, VCAM-1 in the livers of seven infants with biliary atresia (BA), suggesting a trigger for an inflammatory reaction.[13] A larger cohort of 28 infants confirmed significant abnormal expression of ICAM-1, VCAM-1, and E-selectin on sinusoidal and biliary epithelium at rates of 50%, 25%, and 10%, respectively.[14]

Maternal chimeric cells were found in high concentrations in the portal and sinusoidal regions of patients with BA. This indicates that maternal lymphocytes cause bile duct damage through a graft-versus-host immune response.[15]

Liver samples obtained from infants with BA showed coordinated activation of genes related to lymphocyte differentiation, particularly those related to T helper 1 immunity.[6]

Polymorphisms that increase CD14 gene expression, which plays a role in bacterial endotoxin recognition, have been associated with biliary atresia (BA) and idiopathic neonatal cholestasis.[17]

Viral infections

In the 1970s, American paediatrician Benjamin Landing suggested a possible common factor in the etiology of choledochal cysts, neonatal hepatitis, and biliary atresia. He pointed to the action of a hepatotropic virus that can cause bile duct damage, also known as 'infantile obstructive cholangiopathy'.[18]

Rachel Moreki et al. initially provided evidence supporting this hypothesis by demonstrating higher antibody titres against REOvirus type 3.[19]

Hepatotropic and non-hepatotropic viruses have been identified as causes of biliary atresia (BA). An analysis of 249 cases of BA over a 16-year period in New York State revealed that the risk of BA was highest in babies born in spring in New York City, while the risk was higher in babies born in autumn outside New York City.[20] Although seasonal clustering of the disease has also been reported, a large participatory study in Japan did not find such a distribution. Multiparity and advanced maternal age have been identified as risk factors for BA.[21]

Reo Virus

Reovirus type III infection of mice causes biliary and liver damage similar to that seen in human biliary atresia (BA). Neonatal infection with reovirus in this animal model results in hepatitis, intra- and extra-biliary epithelial necrosis, bile duct oedema, inflammation, and irreversible luminal obstruction.[22]

Cytomegalovirus (CMV)

Cytomegalovirus is a double-stranded DNA virus that can infect epithelial cells of the common bile duct. Babies with biliary atresia (BA) who are CMV IgM positive exhibit more jaundice and lower survival rates without liver transplantation, in addition to higher aspartate aminotransferase and aspartate aminotransferase-to-platelet ratio index levels.[23]

Rota Virus

Intrahepatic cholangiocytes from patients with both syndromic and non-syndromic BA have a reduced number of primary cilia that are morphologically abnormal. The number of cilia is reduced in rotavirus-infected primary cholangiocytes, suggesting that ciliary abnormalities are part of the pathophysiology of BA.[24]

Toxic Etiologies

The strongest evidence for this hypothesis comes from three reported outbreaks of BA in lambs in Australia in 1964, 1988 and 2007 In each outbreak, during a period of drought, ewes giving birth to affected lambs grazed on previously flooded land. A significant number of lambs were weak, jaundiced, had acolic faeces and eventually died and were diagnosed with BA at autopsy. The putative mechanism is that pregnant ewes ingested a toxin while grazing on previously flooded land.[25]

A new isoflavonoid toxin was isolated from the Dysphania plant harvested in a recent outbreak area in Australia. This toxin caused severe damage to the extrahepatic biliary tree in a zebrafish model and also loss of cilia in neonatal mouse cholangiocytes. This evidence suggests that an environmental toxin may play a role in some cases of BA.[26]

Environmental Factors

Environmental factors that may trigger biliary atresia include drugs used during pregnancy (amphetamines and alcohol), agricultural and industrial toxins, phytotoxins and mycotoxins.[27]

Vascular Abnormalities

The biliary tree receives its blood supply mainly from the arterial system and impaired arterial flow leads to necrosis in the biliary tree. When compared with healthy infants and other infants with cholestatic diseases, tortuous hepatic artery branches and thickened wall with medial hypertrophy are observed in all patients with BA.[28]

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Current Clinical Approach to Biliary Atresia

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Abstract

Biliary atresia (BA) is a leading cause of liver transplantation in children, characterised by neonatal fibroobliterative disease of the extrahepatic biliary tree. BA may be associated with laterality anomalies and congenital malformations that affect prognosis. Clinical findings include jaundice, acholic stools and organomegaly. The differential diagnosis includes several cholestatic diseases.

Diagnostic biomarkers such as interleukin-33 and matrix metalloproteinase-7 are promising in the detection of BA. Imaging modalities such as ultrasonography and hepatobiliary scintigraphy aid in the diagnosis. Liver biopsy and intraoperative cholangiography are essential to confirm BA and guide the Kasai procedure, the gold standard intervention.

Postoperative markers of successful hepatoportoenterostomy (HPE) include colicky stools, decreased bilirubin, weight gain and decreased pruritus. Patient management includes choleretics (UDCA), nutritional support, prevention of cholangitis and monitoring for complications such as portal hypertension. Liver transplantation may be indicated in certain cases.

Timely and accurate diagnosis of biliary atresia is crucial for effective intervention. The Kasai procedure, if performed promptly, may improve outcomes. Continuous monitoring, nutritional support and appropriate management of complications contribute to a better prognosis. In cases where liver transplantation is indicated, preparation should begin, taking into account the patient's age and weight for optimal outcome.

Key words: Child, biliary atresia, liver transplantation

Introduction

Biliary atresia (BA) is the most common cause of childhood liver transplantation, presenting as a progressive, idiopathic, fibro-obliterative disease of the extrahepatic biliary tree in the neonatal period. Biliary atresia may be associated with laterality anomalies such as situs inversus, asplenia and other congenital malformations (10-15%). The prognosis of BA associated with these malformations is worse.[1-4]

Clinical Findings

Babies with biliary atresia are usually born at term with a normal birth weight. Initially, they show a healthy development. Jaundice develops in the first 8 weeks. It is unlikely to occur later. Total and direct bilirubin levels should be checked in every baby with prolonged neonatal jaundice. On physical examination, acholic stools, dark urine and organomegaly are frequently found. The family is usually not aware of acholic stools. It should be analysed in the anamnesis. Stool colour scales can be used in the evaluation of acholic stools. The sensitivity and specificity of stool colour scales in the detection of BA are 76.5% and 99.9%, respectively.[5-8]

A direct bilirubin (D.bil) value >0.45mg/dL in the first 3 days of life has low specificity (15.4%) and high sensitivity (100%). A D.bil value >1 mg/dL between 3-60 days has 100% sensitivity and 77% specificity for BA. Serum aminotransferases (AST, ALT) are mildly or moderately increased, while alkaline phosphatase (ALP) and gamma glutamine transferase (GGT) are disproportionately increased. In the late period, impairment in liver synthesis functions [hypoalbuminaemia, prothrombin time (PT) and International Normalised Ratio (INR)]may be found to be high.[9-11]

Differential Diagnosis:

Other cholestatic diseases of the newborn should be considered in the differential diagnosis.

Alagille syndrome should be considered in the presence of atypical facial appearance (wide nasal root, triangular face), congenital heart disease and butterfly vertebrae. Galactosemia should be considered in the presence of cataract with cholestasis.

Familial intrahepatic cholestasis (PFIC) should be considered in the presence of cholestasis, excessive pruritus, xanthomas and skin abrasions.

Peroxisosomal diseases, hypothyroidism and genetic metabolic diseases should be considered in the presence of hypotonicity and cholestasis.

In cholestasis developing after total parenteral nutrition, TPN-associated cholestasis should be considered. Infectious diseases should be considered in the presence of fever and weaning.

ARC syndrome should be considered in the presence of limb anomalies, renal pathology and cholestasis, and Aagenez syndrome should be considered in the presence of angioedema and cholestasis.

Tyrosinaemia should be considered in a patient with cholestasis in the presence of marked elevation in INR and AFP, tubulopathy and consanguinity. Neonatal haemochromatosis should be considered in the presence of cytopenia and high ferritin in a newborn with cholestasis.

Diagnostic Biomarkers

Interleukin-33: A study conducted among 30 healthy groups with 60 cholestasis (BA + Other) reported to be able to detect BA with 95% specificity and 96.7% sensitivity.

Matrix metalloproteinase-7 (MMP-7)

In 135 cholestatic and healthy infants, the diagnostic sensitivity and specificity were 98.67% and 95.00%, respectively. The negative predictive value was reported as 98.28%.

In a study of 288 patients with cholestasis, the sensitivity, specificity, positive predictive value and negative predictive value for BA were 95.19%, 93.07%, 97.27% and 91.43%, respectively.

Recommended threshold values differ between these studies.

Levels are affected by conditions such as age, gender and infection.

More comprehensive studies are needed to include these markers in the cholestasis algorithm.[12-17]

Imaging Methods

Abdominal USG

Ultrasonography (USG) may be guiding in the diagnosis of BA. Specific USG findings for BA are as follows.[5,18-23]

- Absence, irregularity, contractility of the gallbladder
- Absence of choledochal
- Triangular cortical sign (specificity 0.95 and sensitivity 0.68)

Hepatobiliary Scintigraphy

Visualisation of the biliary tract can be achieved by using the radioactive substance HIDA (99mTc-hepatic iminodiacetic acid).

The likelihood of BA is very low in patients in whom the passage of the radioactive substance into the small intestine has been demonstrated.

If the patient has absence of gallbladder and choledochal duct on USG and has acholic faeces, it will be more appropriate to give cholangiography without wasting time with scintigraphy.[24,25]

Liver Biopsy

It is done for two reasons

- Demonstration of pathological findings consistent with biliary obstruction supporting BA
  - Bile duct proliferation, enlarged portal ducts, portal duct oedema, fibrosis and inflammation. Canalicular and bile duct plugs are involved.[26,27]
- To differentiate BA from other intrahepatic biliary tract pathologies that do not require surgical intervention.
  - Bile blood deficiency (Alagille syndrome), periodic acid-Schiff (PAS) positive diastase-resistant granules (compatible with alpha-1 antitrypsin deficiency), loss of MDR3 staining (suggestive of PFIC3) or giant cell hepatitis without duct proliferation.[26,27]

Intraoperative Cholangiography

- It is the gold standard diagnostic method in the diagnosis of BA.
- Simultaneous liver biopsy is recommended if not previously performed.
- If BA is confirmed, Kasai procedure should be performed.

Babies with suspected BA should be evaluated rapidly. Because the success of surgical intervention gradually decreases with advancing age. Therefore, necessary investigations for differential diagnosis should be performed within 3-4 days in infants older than 6 weeks and intraoperative cholangiography should be performed. Kasai hepatoportoenterostomy (HPE) is recommended for all infants diagnosed with biliary atresia. It should preferably be performed before <2 months. While success increases in younger children, the chance of success gradually decreases with advancing age >2 months.[28]

Markers of successful HPE[29]

- The patient's colicky defecation,
- D.bil values of 2 mg/dL 3 months after the operation,
- Ensuring weight gain,
- Regression of itching.

Patient management after HPE

Choleretics (UDCA)	It is a hydrophilic bile acid and has been shown to stabilise membranes, reduce free radical formation and increase bile viscosity. In several large, randomised, double-blind, placebo-controlled studies in patients with primary biliary cholangitis, UDCA has been shown to reduce plasma levels of aminotransferases and improve liver histology and quality of life. It has also been reported to reduce the risk of death and the need for liver transplantation.[30-32]
Nutrition and vitamin support	Hypercaloric and MCT-containing nutrition and fat-soluble vitamin supplementation are recommended. Growth should be ensured as it is better in babies weighing >10 kg compared to smaller babies.[33,34]

Prevention of cholangitis	Although the success of prophylactic treatment has been emphasised in randomised controlled trials, we recommend antibiotic prophylaxis until at least 1 year after HPE, although a recent meta-analysis failed to show a cholangitis-reducing effect of prophylaxis.[35-37]
Glucocorticoid use	Clinical evidence does not recommend the routine use of glucocorticoids after HPE in patients with BA.[38,39]
Management of portal hypertension (PHT) and late sequelae	PHT may develop in approximately one-third of patients after successful HPE. Therefore, it should be closely monitored for ascites, peritonitis, and variceal bleeding, and an endoscopic evaluation should be performed annually. Endoscopic ablation of varicose veins should be started after the first variceal bleeding.[40]

Indications for liver transplantation in patients with biliary atresia;[38,41-43]

- Primary failure of HPE
- Total bilirubin >6 mg/dL three months or more after HPE
- Malnutrition
- PHT complications (Recurrent variceal bleeding, ascites, subacute bacterial peritonitis)
- Hepatopulmonary syndrome
- Portopulmonary HT
- Persistent itching
- Refractory coagulopathy
- Recurrent cholangitis
- Hepatocellular carcinoma

Since the results of liver transplantation are better in babies weighing >10 kg compared to younger babies and the chance of success is higher over the age of >2 years, liver transplantation can be postponed if the patients can grow and are clinically and laboratoryly stable.[44]

Prognosis

Most patients with biliary atresia (60-80%) eventually need a liver transplant. A minority of patients who undergo Kasai portoenterostomy survive to age 20 or longer. In most of these patients, complications of cirrhosis and portal hypertension develop and the need for liver transplantation arises.

Conclusion

As a result, acholic stools should be questioned in every patient complaining of jaundice during the neonatal period. If GGT is elevated and there are findings supporting BA on abdominal USG, intraoperative cholangiography should be performed without wasting time. Kasai procedure should be performed immediately in patients with cholangiographic findings compatible with biliary atresia. After the HPE, patients should be closely monitored clinically and laboratoryly. If the HPE is unsuccessful, it should be closely monitored for complications of portal hypertension. Necessary nutritional support should be given for growth, vaccinations should be done regularly, and if possible, the patient should be made to weigh >10 kg or grow up to >2 years of age. Liver transplantation preparation should be made in patients with liver transplantation indication.

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Liver Histopathology in Biliary Atresia

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Abstract

Biliary atresia is an idiopathic, progressive fibroinflammatory cholangiopathy involving the extrahepatic biliary tree in infants. It is one of the most important causes of neonatal cholestasis. If left untreated; can progress to micronodular biliary cirrhosis and death can occur in very early years. Therefore, early diagnosis and timely administration of Kasai portoenterostomy are important for the long-term functioning of the native liver.

Liver biopsy is the most reliable tool for the prelaparotomy diagnosis of biliary obstruction. The diagnostic histopathological features are mild to moderate portal edema with mixed inflammation, ductular reaction, and bile plugs .

The ethiological spectrum of neonatal cholestasis is wide and there are more than 100 diseases identified. Because early diagnosis and treatment is crucial, distinguishing biliary atresia from other causes of neonatal cholestasis is very important. For this reason, the diseases included in the differential diagnosis should be examined correctly with a multidisciplinary approach.

Key words: Biliary atresia, histopathology, neonatal cholestasis

Introduction

Biliary atresia (BA) is an idiopathic, progressive fibroinflammatory cholangiopathy involving the extrahepatic biliary tree in infants. It results in obliteration of the bile ducts leading to ineffective bile flow and chronic liver damage.[1,2] The damage begins in the extrahepatic bile ducts, but in the later stages of the disease, the intrahepatic bile ducts are also damaged. It manifests in the neonatal period, and accounts for approximately %30 of cases of neonatal cholestasis.[3] If left untreated; can progress to micronodular biliary cirrhosis and death can occur by 1-2 years of age.[4]

In infants with prolonged (>2 weeks) jaundice, acholic stools, and dark urine, an extensive investigation should be done.[3,5] In addition to laboratory investigation (conjugated hyperbilirubinemia with elevated GGT), ultrasound, hepatobiliary scintigraphy, liver biopsy and intraoperative cholangiography may be used.[3,4]

Early diagnosis and the correct timing of Kasai portoenterostomy are important for the long-term functioning of the native liver. Although Kasai procedure is not a definitive treatment method, it is important in terms of delaying the time to transplantation. Kasai operation was introduced to the medical literature by Japanese peadiatric surgeon Morio Kasai in 1955 and it is still the only accepted early treatment method.[4,6] Kasai portoenterostomy is based on resection of the fibrotic porta hepatis and then anastomosis of the hepatic hilum with the jejunal loop. Unfortunately, not all Kasai operations are successful. Failure to restore bile flow and/or late diagnosis leads to persistence of jaundice and hyperbilirubinaemia , and progressive cholestatic disease and cirrhosis of the liver. In this case, the only treatment method is liver transplantation.Biliary atresia is the most common cause of pediatric liver transplantation worldwide.[7,8]

Biliary atresia is classified as fetal and perinatal types according to whether it is congenital or acquired and morphologically as Type 1, Type 2a, Type 2b and Type 3 according to the location of obstruction of the extrahepatic bile duct.[9,10] Type 3 is the most common form (90%) and fibrosis in the porta hepatis and atresic/hypoplastic gallbladder are observed. There is also a classification consisting of 4 subgroups: isolated, syndromic, cystic and CMV-associated which was proposed by Davenport.[10]

Histopathology

Liver biopsy is the most common specimen submitted for pathologic evaluation of neonatal cholestasis.[1] It is the most reliable tool for the prelaparotomy diagnosis of biliary obstruction more than 90% of cases.[11,12] However some histopathological features may overlap with those of non-obstructive causes. Because of this a careful examination of the biopsy and clinical workup is necessary.

An adequate neddle-core liver biopsy should be at least 2 cm long, not fragmented, preferably 0.2 mm wide, and contain minimum 10 portal areas.[2] The diagnostic histopathological features are seen in the portal tracts. Mild to moderate portal edema with mixed inflammation, ductular reaction, (ductular proliferation consisting of anastomosing ductules at the peripheral portion of the portal tract accompanied by inflammatory cells) and bile plugs are the main characteristic findings. Fibrosis is observed in varying degrees according to the time of the biopsy. Lobular hepatocellular and canalicular cholestasis starting from the pericentral area is observed. In addition, focal hepatocellular giant cell formations, scattered extramedullary haematopoiesis and balloon degeneration may also be seen. Histopathological changes are typically milder when the sampling time is <30 days of age and may result in a falsely negative diagnosis.[3,4,13] False- negative diagnosis may also be the result of inadequate biopsies.[3] In this situation; repeated biopsies are advised if BA diagnosis persists in the clinical diagnosis. While mild fibrous portal expansion is seen in the early period; porto-portal fibrous bridging is seen especially after the 2nd month; advanced fibrosis and nodulation can be seen in biopsies taken in the later period (>90 days).[4] Immunohistochemical staining for CK7 or CK19 may be helpful in demonstrating the ductular proliferation.[3]

Pathologic examination of the Kasai specimen shows partial or complete fibrous obliteration of the extrahepatic bile ducts, periductular chronic inflammation, myofibroblastic proliferation, and ductal remnants focally may be lined with cubic or columnar epithelium.[4] Gall bladder is often hypoplastic/atretic and demonstrates partial or complete loss of the smooth muscle layer accompanied by mucosal chronic inflammation in the wall.[4]

Macroscopic examination of the explanted specimen shows two different scenarious. In patients who did not receive a Kasai operation or had an unsuccesful Kasai procedure, a firm, greenish liver with typical features of micronodular cirrhosis is seen. On the otherside , the ones who had a succesful Kasai operation and survived with their native livers for several years, prominent perihiler regenerative nodules can be present.[1,14] Microscopic examination of the specimens of the first group is consistent with the macroscopic findings demonstrating biliary cirrhosis with broad fibrous bands in a jigsaw patern.[1] Progressive loss of intrahepatic small bile ducts are seen in untreated cases and in most cases despite the treatment in the long term.[12] Majority of the patients with a succesful Kasai procedure develop portal hypertension in the long term which lead to transplantation. Microscopically a distinct pattern of fibrosis located peripherally can be obtained in the majority of patients . Hepatocellular regenerative nodules around the hilum, biliary cirrhosis and hepatoportal sclerosis features in the portal tracts can also be seen.[15] Dilated large ducts with ulceration of epithelium, bile sludge in the lümen, and bile lakes with inflammatory fibrous wall can be identified.[12] There are multiple theories for the formation of biliary cysts and lakes. One is the association with the ductal plate malformation. The others suggest that the ongoing inflammatory reaction results in cholangitis and bile cyst formation.[12]

Patel et al showed that biliary atresia patients with succesful Kasai portoenterostomy transplanted at adulthood show features of obliterative portal venopathy.[16] They demonstrated in this study that cholestasis and biliary cirrhosis are related to recurrent cholangitis. And in the absence of biliary cirrhosis portal hypertension may be secondary to obliterative portal venopathy.[16]

Differential Diagnosis

The ethiological spectrum of neonatal cholestasis has evolved over time and there are more than 100 diseases identified. The diseases other than biliary atresia with conjugated hyperbilirubinemia include genetic causes, infections, neonatal hepatitis, and structural disorders.[4] Prematurity, total parenteral nutrition, drugs and toxins also can lead to a similar clinical presentation.[4] Because early diagnosis and treatment is crucial, distinguishing biliary atresia from other causes of neonatal cholestasis is very important.

The obstructive ethiologies for cholestasis are choledochal cysts, tumors and stones. They can be differentiated on the clinical, laboratory and radiological data.[3] Cystic biliary atresia is a rare type of biliary atresia that is easily confused with choledochal cyst.[17] The patients with choledochal cyst usually have a regular gallbladder size, and a smooth wall with normal thickness. Lobeck et al. demonstrated that cystic BA cysts typically lacked epithelium and inflammation; cyst walls had an inner, dense cicatricial layer associated with myofibroblastic hyperplasia .On the other hand, choledochal cysts in patients had mostly preserved uninjured epithelium and did not have a subepithelial fibrous tissue.[18]

While the histopathological features of BA are well established, there is a significant histopathologic overlap with the non-obstructive causes of cholestasis.With the increasing use of molecular studies, there are lots of genetic diseases described which show the histopathological distal obstruction pattern seen in BA.

Alpha 1 antitrypsin (A1AT) deficiency is one of the most common genetic diseases of the liver in childhood. It is usually associated with PiZZ phenotype. In the infant period, a cholestatic picture mimicking neonatal hepatitis or BA such as jaundice, acholic stools and high GGT level is seen. Histopathological features are variable and may include damaged bile ducts, ductular cholestasis, ductular proliferation, portal chronic inflammation, ductular paucity, parenchymal giant cells and fibrosis. It should be kept in mind that the characteristic dPAS-resistant globules may not be very prominent in the first 3 months. If a liver biopsy showing an obstructive biliary pattern is from an infant, A1AT deficiency should always be considered in the differential diagnosis. In older children (>3 months), absence of fibrosis on biopsy and dPAS positive globules are useful in differentiation from BA.[3-5]

Progressive familial intrahepatic cholestasis is a group of autosomal recessive genetic disorders characterized by chronic cholestasis and variable progression to liver failure and cirrhosis.[4] There are 6 types identified; and all except type 3 have low GGT levels. So the type 3 mostly resembles the BA both on clinical and pathological features. The disease is characterized by abnormal canalicular transportation and secretion of the bile acids.[4] PFIC-1 , also called Bylers disease, is characterized by mutations in the ATP8B1 gene. Liver biopsy shows bland canalicular and hepatocellular cholestasis without a distinct obstructive pattern. PFIC-2, harbors a mutation on the gene(ABCB11) that encodes bile salt export pump (BSEP) protein. On histopathological examination of the liver biopsy, a giant cell hepatitis pattern and immunohistochemical loss of canalicular BSEP staining will be helpful. PFIC-3 is caused by mutations in the ABCB4 gene. This mutation results in the loss of function of phospholipid transporter MDR3 on the hepatocytes. Liver biopsy shows portal edema, mixed inflammation, ductular reaction and bile plugs that closely mimics BA's pathologic findings. But, MDR3 immunohistochemistry may be helpful for the diagnosis. In the clinical context it is very rare, that a PFIC-3 patient presented with a persistent neonatal cholestasis.[4]

Also it should kept in mind that weak or normal expression of BSEP and MDR3 can be seen in missense mutations; and it does not rule out functional deficiency.[19]

Paucity of intrahepatic bile ducts includes 2 groups; syndromic (Alagille) and non-syndromic variants. Alagille syndrome is an autosomal dominant disorder characterized by mutations in the JAG gene in more than %95 of the cases. It is associated with heart, vascular abnormalities, spinal abnormalities (butterfly vertebra), facial dysmorphism, ocular and renal abnormalities.[3-5] It is characterized by the reduced number of the bile ducts in the portal tracts. The loss of the bile ducts should be identified in >50% of portal tracts in an adequate biopsy consisting of 10 portal areas.[4] Histopathogical findings vary by the age of the patient and the progression of the disease. Ductular proliferation is usually lacking but it can be seen in early biopsies leading to confusion with BA. Progression to cirrhosis is slower than BA.[3]

There are lots of metabolic and genetic diseases including cystic fibrosis, bile acid synthesis defects, disorders of carbonhydrate metabolism, lipid metabolism, aminoacid metabolism, copper metabolism, mitochondropathies, etc. that can present with neonatal cholestasis mimicking BA.[4] The liver biopsy can be normal or show the features of the specific disorder.[4] The clinical and genetic investigations should be evaluated together.

Idiopathic neonatal hepatitis shows a giant cell hepatitis pattern on biopsy. Giant cell transformation of hepatocytes is a nonspesific reactive change.It can be seen due to very different aetiologies ranging from infectious diseases to genetic/metabolic diseases. Histopathologically, predominant lobular or canalicular cholestasis, extramedullary hematopoesis, and variable inflammation are seen. The histopathological features such as distinct ductular reaction, bile plugs, portal fibrosis, absence of sinusoidal fibrosis,and abnormal imaging findings of extrahepatic biliary tract support BA.[3,4,20]

One of the differential diagnosis of diseases with features of obstructive cholestasis is total parenteral nutrition – related hepatopathy. Cholestasis may occur within 2 weeks of TPN therapy and may mimick BA on histology. Liver biopsy shows portal edema, mixed inflammation, ductular reaction, bile plugs, lobular cholestasis and microvesicular steatosis.[4, 21] Increasing portal fibrosis may be seen in infants who receive TPN more than 6 weeks.[4] Clinical history of TPN should always be excluded before making a diagnosis of BA.

It has been shown that it is not possible to differentiate BA from TPN-associated hepatopathy and A1AT deficiency by biopsy alone without sufficient clinical information and the importance of clinical collaboration has been emphasized.[2]

Conclusions

BA is a neonatal disease characterised by idiopathic progressive fibroinflammatory obstruction of the extrahepatic biliary tract. Classical histopathological findings include portal edema, mixed inflammation, ductular reaction, biliary obstruction, and variable degrees of fibrosis in later stages. Early diagnosis and treatment contribute to prolonged liver survey. Recurrent episodes of cholangitis may lead to Kasai procedure failure. It should be kept in mind that obliterative portal venopathy and nodular regenerative hyperplasia are the features other than cirrhosis that may be seen in the explant specimens of transplanted patients after successful Kasai operation. Neonatal cholestasis has a wide spectrum of differential diagnosis and the diseases included in the differential diagnosis should be examined correctly with a multidisciplinary approach.

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Diagnostic Radiological Findings in Biliary Atresia

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Abstract

Biliary atresia (BA) is responsible for more than 90% of cases of obstructive biliary obstruction. It is of great clinical importance to rapidly and accurately differentiate biliary atresia from other causes of neonatal cholestasis. As it is a serious and progressive disease, early diagnosis is crucial for successful treatment. The ideal diagnostic tool for the differentiation of cholestatic jaundice in infants should be accurate, reliable, non-invasive and easily accessible. Among the diagnostic methods, USG is the first examination, MRCP is used as a problem solver. This presentation will review radiological imaging techniques and radiological findings used in the diagnosis of BA.

Keywords: Biliary atresia, pediatric, Ultrasound, MRCP

Presentation

Biliary atresia (BA) is the most common surgical cause of neonatal cholestasis. Its prevalence varies between 1/5,000-20,000 depending on the geographical region. Although the aetiology is unknown, viral infections, toxins and genetic factors have been implicated.[1] To improve outcomes in patients with BA, diagnosis and surgery should be performed as soon as possible.

The Kasai classification, also known as the Japanese and Anglo-Saxon classification, is an anatomical classification of the level and severity of obstruction in patients with BA.[2] In this classification, obliteration of the main bile duct (patent cystic duct and main hepatic duct) is observed in Type I, whereas obliteration of the main hepatic duct (patent cystic duct and main bile duct) is observed in Type II-a. In Type IIb, obliteration of the main hepatic duct, cystic and common bile duct is observed. In Type III, obliteration of the left and right main hepatic ducts is observed at the level of the porta hepatis. The most common type is type 3 and is seen in 90% of cases. BA is further divided into two types: non-syndromic form (80%) and syndromic form (20%). Syndromic BA may be associated with various congenital anomalies such as polysplenia or asplenia (100%), situs inversus (50%), preduo-

denal portal vein (60%), absence of retrohepatic inferior vena cava (40%) or cardiac anomalies (50%).[3]

Rapid and accurate differentiation of BA from other causes of neonatal cholestasis is of great clinical importance. Patients with BA should be operated on as soon as possible to improve surgical outcomes. Among radiological diagnostic methods, ultrasound (US) is used as a first-line screening method because it is cost-effective, does not use ionising radiation, is a real-time examination and generally does not require sedation. The use of microconvex or linear US probes with the highest frequency allows us to achieve good spatial resolution. The examination should be done after 4 hours of fasting.

Prenatal diagnosis of BA is extremely rare. Findings detected in fetuses with BA include inability to visualize the gallbladder, irregular gallbladder walls, cyst in the liver hilus, and heterotaxy syndrome. It is rare for the fetal gallbladder not to be permanently visualised. 15-43% have isolated gallbladder agenesis, a benign condition. The lack of visibility of the gallbladder lumen or the presence of an atretic gallbladder are the main findings on US in newborns with BA. Shape and wall abnormalities have been described for the atretic gallbladder. Reduced gallbladder size (less than 15-19 mm), irregular wall, unclear and irregular mucosa are findings known as the gallbladder ghost triad.[4,5] (Fig. 1) Lack of gallbladder contractility is another finding identified in BA, and it has been observed that the bladder volume measured before and after feeding decreases by 67-86%. It has been observed that this stenosis may be wider and some patients with LBP also have normal contraction.[6]

The triangular cord sign is in the form of a triangular or tubular echogenicity representing the fibrotic remnant of the extrahepatic biliary tree observed, just anterior distal right portal vein in the BA. The triangular cord sign has become accepted as an important diagnostic feature. If the echogenicity area is >3-4 mm, it is reported as positive. The triangular cord sign has been shown to be present in 17% of infants younger than 30 days and in 56% in the older group. This is thought to be due to the fact that the disease is a progressive disease.[7,8] Examining the accuracy of various ultrasound findings in the diagnosis of BA, it is known that the diagnostic accuracy increases when the triangle cord sign and gallbladder abnormalities are evaluated together.[9]

Cysts observed in BA are divided into two types. Macrocysts are observed in the hilus and vary between 0.5-4.0 cm in diameter, while microcysts are small cysts with dimensions less than 0.5 cm and are located at the junction of the intrahepatic bile ducts, at the porta hepatis, in the same region as the triangular cord sign. Macrocysts can also be seen in prenatal diagnosis. BA accompanied by macrocysts, also called cystic biliary atresia, is a relatively rare subtype.

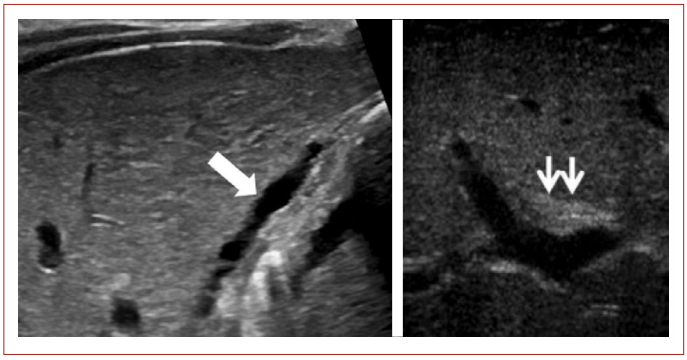

Figure 1. Irregular wall and triangular cord findings of atretic gallbladder on USG examination.

Common bile duct cyst is included in the differential diagnosis of cystic biliary atresia. The absence of intrahepatic ductal dilatation and the presence of a triangular cord sign or gallbladder abnormality in a patient with a cyst in the portal indicate a diagnosis of BA. Mud/stone within the cyst is more common in choledochal cysts.[10,11]

Studies have shown that the diameter of the hepatic artery increases in children with BA compared to normal controls or children with hepatitis. Hepatic artery diameter/portal vein diameter >0.45 or hepatic artery diameter greater than 1.5 mm predicts the diagnosis of biliary atresia. However, in the BA group younger than 30 days, the hepatic artery diameter was found to be significantly smaller than in older than 30 days with larger BA. It is thought that this is due to the fact that BA is a progressive disease and the portal flow is reduced over time due to the development of cirrhosis.[12,13] Additionally, hyperplastic and hypertrophic changes in the branches of the hepatic artery can be detected in the hepatic subcapsular area. This phenomenon has also been proposed as a diagnostic criterion for BA.[14] However, there is no measurement available for an objective evaluation. Although liver stiffness measurements by elastography are significantly higher in patients with BA compared to infants with other causes of cholestatic jaundice, there is no cut-off value to distinguish cirrhosis from other causes of cirrhosis. Elastography has been shown to improve diagnostic performance in prognostic assessment, especially in infants >30 days old. However, gray scale US is known to have better diagnostic performance than elastography for BA.[15]

Common bile duct visibility also contributes to the diagnosis of BA. However, it may not be visualised in ultrasound scans of newborn, even though it is usually normal. In particular, the absence of visualization of extrahepatic bile ducts by Magnetic Resonance Cholangiopancreatography (MRCP) is diagnostic of BA. Visibility of part of the extrahepatic bile duct does not exclude BA. It may not always be possible to see the entire extrahepatic biliary tree, from the right and left hepatic branches to the distal common bile duct.

MRCP is used as a problem solver in the diagnosis of BA due to its high cost and the need for sedation. It is recommended to fast for at least 4 hours before examination. Fast spin echo three-dimensional (3-D) taken with the fat suppression technique and coronal images allow smaller structures to be detected and evaluated without distortion. Real-time navigator gating is necessary to synchronize breathing. Field of view 18–24 cm and acquisition matrix 256×256 are adequate. Using a flexible surface coil according to the child's weight (minimum 12 channels) is suggest. The combination of MRCP and ultrasonography increases the diagnostic accuracy of BA. Again, failure to visualize the gallbladder identified on USG, bladder size and wall abnormalities, and a high signal area equivalent to the triangular cord finding in the porta hepatis can be detected on T2-weighted images (Fig. 2).

Differentiation of biliary atresia from neonatal hepatitis, which should

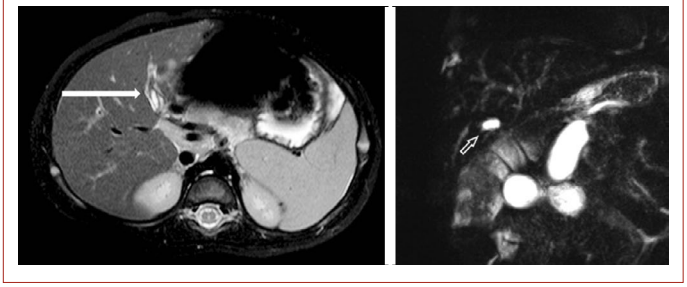

Figure 2. Atretic gallbladder in T2A axial and MRCP coronal sections.

be considered in the differential diagnosis, is made by a normal gallbladder length and morphology, the presence of post-feeding contraction, and the absence of other features suggestive of BA. Gallbladder wall thickening or periportal edema may occur. In addition to cardiac, ocular and skeletal abnormalities, a small gallbladder may be seen in Aagille syndrome, where interlobular bile ducts (PILBD) deficiency, typical facial appearance is observed, or the extrahepatic biliary tree may not be visualized on MRCP. It is distinguished by the absence of Triangular cord sign and hepatic artery dilatation, as well as the presence of systemic findings.

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Diagnostic Nuclear Medicine Examinations in Biliary Atresia

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Abstract

Early diagnosis and initiation of treatment are very important in biliary atresia. Radiologic and nuclear medicine imaging is very crucial in the diagnosis. Tc-99m iminodiacetic (IDA) derivatives are used in scintigraphic imaging. Tc-99m sestamibi (MIBI) is another radiopharmaceutical that can be used in wall biliary tract imaging. While it has the important advantage of having little effect on bilirubin level, caution should be exercised in false negative reporting due to direct secretion into the colon at the 2nd hour and beyond. We think that biliary scintigraphy remains important in the multidisciplinary approach in the diagnosis and follow-up of biliary atresia.

Key words: Biliary atresia, scintigraphy, radiopharmaceuticals

Biliary atresia (BA) is a disease that manifests itself with prolonged jaundice in infancy, significantly impairs life expectancy and quality of life, thus early diagnosis and initiation of treatment are important. Radiologic and nuclear medicine imaging is very crucial in the diagnosis.

Tc-99m-diisopropyl-IDA (DISIDA) and Tc-99m-trimethylbromo-IDA (mebrofenin), which are Tc-99m iminodiacetic (IDA) derivatives, are used in nuclear medicine imaging. Hepatic extraction of technetium-99m DISIDA is 88%, urinary excretion is 11% and hepatocyte uptake is 36% when bilirubin levels > 20 mg/dl. Hepatic extraction of Tc-99m mebrofenin is 98%, urinary excretion is 2% and hepatocyte uptake is 70% when bilirubin levels are > 20 mg/dl. Tc-99m mebrofenin should be preferred in cases with high bilirubin levels.[1]

Phenobarbital is given perorally at a dose of 5mg/kg/day for at least 3-5 days in order to increase bilirubin excretion by inducing microsomal enzymes in infants under 45 days of age. In preterm babies, this period can be extended up to 90 days. Sedation is not needed. It is preferred that the injection is given just before feeding time to initiate dynamic imaging.[2]

MR cholangiography is another noninvasive imaging method used in the diagnosis of biliary atresia. However, high cost and the need for sedation prevent its routine use. Failure to visualize extrahepatic bile ducts during MR cholangiography reveals biliary atresia[3] with 90% sensitivity and 77% specificity.[4]

During the study period, 93 patients aged 10 to 110 days with cholestasis and suspected Biliary Atresia underwent EHIDA. Sensitivity and NPV were 91.2% and 85.3%, specificity and PPV were 80.6% and 88.1%.[5] These results showed that EHIDA was sub-optimal in both the diagnosis and exclusion of BA 68Gallium-labeled tetrabromophthalein ([68Ga]Ga-BP-IDA) is a new radiopharmaceutical used in PET/CT and is promising due to its high resolution.[6]

Tc-99m sestamibi (MIBI) is a cationic lipophilic agent that is a sub-

strate of P-glycoprotein. This glycoprotein is normally expressed on the bile canalicular surface of hepatocytes. This feature provides a different mechanism of hepatic excretion from bilirubin excretion. While it has the important advantage of having little effect on bilirubin level, caution should be exercised in false negative reporting due to direct secretion into the colon at the 2nd hour and beyond.

Sdeghi et al. evaluated the value of Tc-99m BrIDA and Tc-99m MIBI in the differential diagnosis of neonatal cholestasis in 20 infants (10 with extrahepatic biliary atresia and ten with neonatal hepatitis) with a mean age of 2.41 months (range, 0.1-5 months). Tc-99m MIBI scintigraphy showed intestinal activity in all patients, including patients with biliary atresia.[7] Increasing small bowel activity in the area between the two renal pelvises corresponding to the jejunum in the early images leads away from the diagnosis of biliary atresia.

The hepatic extraction fraction value of Tc-99m IDA biliary tract scintigraphy in the first month after Kasai portoenterostomy can be used as a valuable parameter in long interval scintigraphic follow-up.

We think that biliary scintigraphy remains important in the multidisciplinary approach in the diagnosis and follow-up of biliary atresia.

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Kasai Portoenterostomy and Outcomes in Biliary Atresia

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Abstract

Biliary atresia is a progressive and obstructive kronik inflamatuar disease of the bile ducts. Kasai portoenterostomy has been used in its treatment since 1959. The most important factors in the success of the Kasai procedure are the age of the patient and the experience of the surgeon and whether complications occur in the early period. Staining the acholic stool with bile and decreasing bilirubin levels in the early postoperative period are considered success criteria. Studies have reported that the 5-year survival rate with native KC after the Kasai operation is around 50%.

Key words: Bilier atresia, Complications, Kasai portoenterostomi, Outcome

Biliary atresia is a bepatobiliary disease characterized by progressive inflammation and fibrous obstruction of the bile ducts. The gold standard method still for diagnosing biliary atresia is an intraoperative cholangiogram with concurrent liver biopsy. It should not be forgotten that the following diagnoses may be encountered during operative cholangiography: Biliary atresia, Biliary hypoplasia, Bile plug syndrome, Choledochal cyst, Intrahepatic bile duct dilatation (Caroli disease), Intrahepatic bile duct atresia (Alagille syndrome), Extrahepatic bile duct perforation.[1,2] Biliary atresia is characterized by progressive inflammatory obstruction of the extrahepatic bile ducts, and current therapeutic management is limited to two surgical approaches: Kasai hepatoportoenterostomy and liver transplantation.[3,4] Kasai portoenterostomy, which is the treatment of biliary atresia described by Morio Kasai in 1959, is still the main treatment method. Today, although there have been minor changes in the original Kasai portoenterostomy, satisfactory progress in surgery has not been achieved.[5]

How do we perform Kasai portoenterostomy?

The abdomen is entered through a subcostal incision on the right side of the abdomen. The initial dissection of the fibrous remnant is begun gall bladder and cystic duct. Next, forward dissection of the fibrous tissue proceeds just anterior to the portal vein and hepatic artery. Dissection should proceed until the fibrous remnant has come into approximation with the capsular surface of the liver within the bifurcation of the portal vein. Exised of the fibrous tissue is then performed. The ligament of treitz should be identified and a point about 15 cm from this should be transected to be the site of the jejunal anastomosis. The bowel is then divided, and a Roux loop, measured along the anti-mesenteric border at approximately 40 cm, constructed. The Roux limb is passed retrocolic and interrupted anastomosis to the transected porta hepatis is made using running absorbable monofilament 6/0 suture.[6]

The rate of complications in the early period (0-6 months) after Kasai portoenterostomy is 45-54.6%.[2,7] Complications of biliary atresia surgery can be evaluated as surgery-related or due to biliary atresia itself. Surgery-related complications include bleeding, anastomotic leak, small bowel obstruction, and internal hernia. Complications associated with biliary atresia include cholangitis, portal hypertension, malabsorption of fat-soluble vitamins A, D, E and K, intrahepatic bile lakes, liver failure, malignancy.[3]

In the literature, 5-year success rates of Kasai portoenterostomy have been reported in the range of 35-85%. The most important factors affecting success are; It is known that the child's age at diagnosis, early period camplications and the experience of the surgical clinic. The use of the stool color card in many countries, including Japan, Argentina, France and Taiwan, has proven to be effective in reducing the age of diagnosis and increasing the success rate of Kasai portoenterostomy.[4,8-10]

The earliest measurable result of the Kasai portoenterostomy is resolution of jaundice. Surgical success was defined as achievement of a total serum bilirubin ≤ 20 micg/dL. In experienced centers, biliary drainage can be achieved in up to 60-67.1% of children after Kasai portoenterostomy. Serum bilirubin of children with adequate bile drainage decreases to normal values within 6 months. 80% of these children can reach adolescence with a good quality of life without liver transplantation.[4,11]

It is reported in the literature that more successful results will be

achieved by lowering the age of diagnosis and collecting biliary atresia cases in a single center.

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Liver Transplantation for Biliary Atresia

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Abstract

Biliary atresia is the leading cause of liver transplantation in patients with biliary atresia. Biliary atresia is a complex disease that requires a multidisciplinary approach. Close monitoring of the patients in terms of nutritional indices, signs and symptoms of portal hypertension, and complications of cirrhosis is necessary. The two-step surgical therapy involving Kasai Porto-enterostomy followed by liver transplantation at an optimal time is the key to obtaining good patient and graft outcomes. The optimal timing is the most controversial point in the management of patients with biliary atresia. If porto-enterostomy results in good bile flow, the transplant-free survival of the patients is very good. However, things do not always go smoothly and there can be an early failure of the Kasai Porto-enterostomy, or cases may be complex and diagnosed later in infancy. In these cases, liver transplantation should be considered early to provide better graft and patient survival. Eventually, all patients with biliary atresia will develop end-stage liver disease and these patients will be transplanted later in life. As the patient's age is older, the success of liver transplantation will increase in this setting. The success of liver transplantation also depends on the nutritional status of the patients, the presence of recurrent cholangitis, and the presence of extrahepatic organ system failure. Physicians must have a good clinical perception to treat patients with biliary atresia.

Keywords: Liver transplantation, living donor liver transplantation, biliary atresia, reduced size grafts

Introduction

Biliary atresia (BA) is progressive inflammatory obliteration of the intrahepatic and extrahepatic bile ducts.[1] The incidence is 1 in 8000 to 18000 live births. Due to progressive obliteration of the bile duct and the recurrent cholangitis attacks the patients experience progressive liver failure and end-stage liver disease is inevitable at the early stages of childhood.[2] It has four main phenotypes:1) Isolated BA, 2) BA associated with laterality defects, 3) BA associated with major congenital malformations, and 4) BA associated with bile duct cysts; also named cystic BA.[1,2] The etiology is multifactorial but abnormal bile duct development, perinatal viral infections, perinatal toxin exposure, and abnormal immune response have been implicated as the main factors in the etiology of BA.[1,2]

The two-stage surgical approach is defined as Kasai porto-enterostomy followed by liver transplantation at an optimal time when liver failure develops. Currently, this is the preferred treatment that provides the longest survival for the patients.[3] Despite all efforts to restore the normal bile flow in patients with BA, it will eventually progress to end-stage liver failure and patients will require liver transplantation.[4] The present study aims to evaluate the role and efficacy of liver transplantation in pediatric patients with BA.

Indications of Liver Transplantation

Indications of liver transplantation for BA are summarized in Table 1.

Table 1. The summary of the main indications for liver transplantation in Biliary Atresia

Indications for Liver Transplantation in patients with Biliary Atresia
Failed Kasai Porto-enterostomy
Late diagnosis of Biliary Atresia
Failure to thrive
Recurrent bacterial cholangitis
Portal Hypertension and its complications
Treatment refractory pruritus
Hepatopulmonary syndrome and porto-pulmonary Syndrome
Hepatorenal syndrome
Development of hepatic malignancy

Failed Kasai Porto-Enterostomy

The prognosis of the patients with BA is poor unless the flow of bile is restored. Occasionally, despite a Kasai Porto-enterostomy, normal bile flow is not restored, and the faith of the patients is not different from patients who are not operated. The patients cannot live longer than two to three years unless liver transplantation is performed.[5-7] Early failure of Kasai Porto-enterostomy is defined as failure to restore normal bile flow in the patients within 3 months following the surgery.[8] A large-volume study from the United States of America has shown that patients who had bilirubin levels less than 2 mg/dL at the postoperative 3rd month following Kasai procedure had a 2-year transplant survival rate of 84% while the patients who had bilirubin levels more than 2 mg/dL had a 2-yea transplant-free survival of 16%.[8] In patients with BA who have undergone liver transplantation, if the bilirubin levels have not dropped below 2 mg/dL the patients should be evaluated for liver transplantation as early as 6 to 9 months of age.[2]

Late Diagnosis of Biliary Atresia

As it is known very well the complications that are encountered during liver transplantation caused by Kasai Porto-enterostomy include bowel perforation caused during adhesions that occurred due to Kasai Porto-enterostomy.[9-15] Some studies showed similar results regarding operative duration, blood loss, intraoperative complications, and duration of hospital and intensive care unit stay.[9-15] Late Kasai Porto-enterostomy is defined as performing the procedure at an age ranging between 90-120 days in patients with a confirmed diagnosis of BA. Studies have shown that the outcome of patients who have undergone late Kasai Porto-enterostomy have poor outcomes in terms of survival with native livers; survival rates at 1-, 5-, and 10-years were approximately 40%, 20%, and 15%, respectively.[16-19]

Failure to Thrive

Patients with BA have serious malabsorption of iron, zinc, lipids, and fat-soluble vitamins.[20] Furthermore, due to recurrent cholangitis attacks and the effects of systemic circulation, the patients experience a severe catabolic process leading to severe protein energy malnutrition.[20, 21] Protein-energy malnutrition and severe malabsorption can occur despite a successful Kasai Porto-enterostomy. Therefore, continuous surveillance of the anthropometric parameters is recommended to determine any growth retardation in early period.[21] Also, these patients experience metabolic bone disease which is defined as brittle bones despite the absence of calcium and vitamin D deficiencies. Patients with BA who develop failure to thrive, protein-energy malnutrition, or metabolic bone syndrome should be evaluated for transplantation.[2]

Bacterial Cholangitis

On average 60% of the patients with BA and who have undergone Kasai Porto-enterostomy develop at least one episode of cholangitis. And nearly 30% of the patients will experience more than one episode of cholangitis.[22,23] Cholangitis reduces transplant-free survival of patients with BA. Furthermore, cholangitis increases the failure rate of Kasai Porto-enterostomy by three years.[24] Liver transplantation should be considered in patients with recurrent cholangitis despite adequate antibiotic therapy, the emergence of multidrug-resistant microorganisms, patients with a history life-threatening sepsis, and patients suffering from cholangitis that severely impairs the quality of life due to frequent hospitalizations and invasive therapeutic interventions.[25]

Portal Hypertension

Portal hypertension is the most frequent complication of end-stage liver disease.[26] Definitive findings of portal hypertension are splenomegaly, hypersplenism, ascites, and varices and the complications related to these spectra of events. Some of the patients show only the complications of splenomegaly and hypersplenism which is also suggestive of portal hypertension.[2] Studies have shown that nearly 70% of the patients with BA have some form of portal hypertension. The causes of portal hypertension are the progressive inflammatory fibrosis of the liver and recurrent cholangitis contribute to the rapid development of portal hypertension in patients with BA. Furthermore, 60% of the patients with BA have one episode of variceal bleeding and nearly 20% suffer from recurrent variceal bleeding.[27] A large-volume study from France analyzed the patients with BA who could survive till adulthood and the results of the study showed that almost all the patients had cirrhosis, nearly 80% had signs and symptoms suggesting portal hypertension.[28] The presence of signs and symptoms of portal hypertension as well as its complications is an indication for portal hypertension.

Pruritus

Pruritus is a common complication of congenital disorders such as Alagille syndrome and Progressive Familial Intrahepatic Cholestasis. However, patients with BA can suffer from in severe pruritus that may have an impact on the quality of life of the patients. First step during the decision-making process is to rule out other causes of pruritus and maximum medical therapy should be performed.[29] In patients with BA and intractable pruritus that have a severe impact on the quality of life, liver transplant should be considered as the preferred treatment.

Extrahepatic Organ Systems Involvement

Hepatopulmonary syndrome results in hypoxia in a patient with portal hypertension and is caused by abnormal intrapulmonary shunting of the blood from right to left side. It can be seen in up to 20% of the patients with BA.[30,31] On the other hand, *porto-pulmnonary hypertension* is defined as increased mean pulmonary artery pressure and increased pulmonary vascular resistance in a patient with portal hypertension. It causes exertional dyspnea, hypoxia, and right-sided heart failure.[32] It is observed in less than 1% of the patients with BA. Hepatopulmonary syndrome is a definitive indication for liver transplantation. On the other hand, mean pulmonary arterial pressure is measured in patients with BA and who suffer from porto-pulmonary hypertension. Mean arterial pressure should be less than 50 mm-Hg to perform liver transplantation.[32]

Hepatorenal syndrome is defined as acute renal failure in a patient with end-stage liver failure who does not have intrinsic renal disease.[33] Liver transplantation should be considered in a patient who develops hepatorenal syndrome.[34]

Hepatic Malignancies

Hepatocellular carcinoma (HCC) develops in the setting of liver cirrhosis.[35] HCC can be observed in less than 1% of the patients with BA and can even be observed in infants. *Cholangiocarcinoma* is very rare in patients with BA.[36] HCC is suspected or confirmed by imaging and pathological analysis, the patients should be enlisted for liver transplantation provided that there is no distant metastasis and macrovascular invasion.[37,38]

Pretransplant Management

Pretransplant management of pediatric patients with BA requires a multidisciplinary approach. *Nutritional surveillance and support* have paramount importance. Anthropometric parameters, biomarkers of nutritional status (albumin, retinol-binding protein, and transferrin), and fat-soluble vitamins, iron, and zinc should be monitored regularly.[39]

For patients with BA who have signs and symptoms of portal hypertension, 90% have *esophagogastric varices* and 30% of the patients experience recurrent variceal bleeding. The mortality of recurrent variceal bleeding is nearly 5%.[40,41] Surveillance endoscopy enables determining patients who progress rapidly from early-stage esophageal varices to advanced-stage esophagogastric varices. Preemptive band ligation and sclerotherapy are effective in treating esophageal varices.[42] However, preemptive variceal treatment in patients with variceal bleeding refractory to band ligation and sclerotherapy should be considered for liver transplantation.[43]

Thrombocytopenia is the most common manifestation in patients with portal hypertension causing splenomegaly and hypersplenism. Platelet replacement is only necessary in patients with variceal bleeding and a platelet count between 20-60x10^3 corpuscles/mm^3.[2]

Another consequence of portal hypertension is *ascites* and *hyponatremia* (<130mEq/L). Ascites is observed in 30% of the patients with BA. The initial step in the medical treatment of ascites is sodium restriction. This may be followed by the use of diuretics such as spironolactone as a single agent or in combination with furosemide. In patients who have a low albumin level 20-25% albumin infusion combined with furosemide may be effective in the treatment of ascites. In cases that do not respond to adequate medical therapy (intractable ascites), large-volume paracentesis can be used (should be less than 200 mL/kg or no more than 680 mL/hr). Paracentesis can be combined with albumin infusion to increase the effective plasma volume.[44]

Fluid restriction is used for the treatment of hyponatremia. In cases with severe hyponatremia (115-120mEq/L) or moderate hyponatremia with neurologic symptoms should be treated with an infusion of normal or hypertonic saline. The increase in the sodium levels of the patients should not increase 9mEq/L per day.[45]

Spontaneous bacterial peritonitis (SBP) can develop in patients with ascites and physicians should have a high grade of suspicion to diagnose SBP in the pediatric population. The most common etiologic agent is Streptococcus pneumonia. Patients with recurrent SBP require prophylactic antibiotics.[46] Prophylactic trimethoprim-sulfamethoxazole therapy may prevent bacterial cholangitis episodes and prolong the transplant-free survival of patients with BA who have undergone Kasai Porto-enterostomy.[46]

Redo-portoenterostomy can be attempted in patients with BA who initially showed a good bile flow following Kasai's procedure but suddenly deteriorated. However, redo-surgeries may complicate future liver transplantation.[47]

Vaccination programs should be completed as much as possible because vaccine-preventable infectious disease is still a major problem in pediatric transplant recipients. The live vaccines should only be performed if the time to transplant is more than 4 months. Tuberculosis surveillance should be performed in high-risk areas.[48]

Timing of Liver Transplantation

According to the United Network for Organ Sharing (UNOS) data pediatric patients with BA who have a pediatric end-stage liver disease score (PELD)≥17 had the best outcome following liver transplantation.[49] However, if the waiting period is too long or if the patients are enlisted at a late stage, the physical condition of the patient deteriorates and may not undergo a major procedure such as liver transplantation and mortality on the waiting list is 25%.[50] Living donor liver transplantation (LDLT) is effective and safe in pediatric patients with BA who have a PELD score between 15 to 25.[51]

We have searched the global literature regarding pediatric patients who undergo liver transplants for BA and the studies have shown that the patients have a mean age of 0.8 to 3.7 years, a mean body weight of 8 to 18.6 kg, and studies report a 10-year graft survival of 70-90%.[52-58] The factors that affect graft survival are donor body mass index, ABO incompatibility, graft type, recipient age, and the experience of the center.[4]

The left lobe liver grafts have poor overall survival when compared to the right lobe liver grafts.[4] Patients older than 18 years of age have better overall graft survival than adolescents and younger children.[4] Centers performing 50 cases of liver transplantation for BA annually are considered experienced centers. The graft and patient survival in experienced centers are better than the inexperienced centers.[4] The age of the patients with BA who undergo liver transplantation in centers performing LDLT is younger age (<5 years) when compared to centers that perform deceased donor liver transplantation (DDLT).[4]

Although Kasai Porto-enterostomy postpones liver transplantation by providing a good liver function, failed Kasai procedure is a risk factor for poor outcomes after liver transplantation.[59]

Comments

Biliary atresia is one of the most common indications for liver transplantation in the pediatric population. A two-step surgical approach including Kasai Porto-enterostomy followed by liver transplantation at an optimal time provides the best outcome for the patients. However, when optimal patient response is not obtained after the initial step of this approach, controversial points arise regarding the possible therapeutic options. However, since the results are discouraging otherwise, liver transplantation should be considered early in these cases. In patients who respond to Kasai's procedure, liver transplantation can be postponed until the patient is in adolescence or early adulthood.

A multidisciplinary approach is necessary to treat these patients. Nutritional support is of paramount importance.

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