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# Biliary atresia recent insight

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ABSTRACT

Biliary atresia (BA) is a rare disease characterized by ascending obstruction of bile ducts that exclusively affects newborn infants. The etiology of the disease is not known. BA is considered to be a phenotype resulting from several pathogenic processes leading to obstruction of the biliary tree. It usually presents shortly after birth, characterized by persistent jaundice, hepatosplenomegaly, clay-colored stool, and dark urine. It affects both the extra-hepatic biliary ducts (EHBDs) and the intra-hepatic biliary system (IHBDs), but the former is more severely affected. Diagnosis of BA is a great challenge and must be achieved as early as possible to delay progression to cirrhosis. Laboratory tests reveal direct hyperbilirubinemia and, variable levels of transaminases, gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase (ALP), which overlap significantly with other causes of neonatal cholestasis. The intraoperative cholangiogram is considered the gold standard for the diagnosis of BA and is performed routinely in many institutions. BA can be divided into correctable and non-correctable types; the former accounts for (10–15%) of cases, in which the proximal common hepatic duct is patent, allowing primary anastomosis of the EHBDs to the bowel. All patients are subjected to identical surgical and medical treatments; consisting of Kasai portoenterostomy (KPE), which entails removal of the atretic extra-hepatic tissue and a Roux-en-Y jejunal loop anastomosed to the hepatic hilum. Kasai portoenterstomy is considered a transition to liver transplantation, as the pathology may be still ongoing. BA is the most frequent indication for liver transplantation in infants, which is the only treatment that can definitively arrest the natural disease course. In conclusion: BA is a serious liver disease that needs to be further studied, and awareness of BA should be increased among the public and health care workers to prevent the complications of this disease.


**Contents**



*Abbreviations:* AP, Alkaline phosphatase; BA, Biliary atresa; BASM, Biliary atresia splenic malformation; CMV, Cytomegalovirus; DDT, Duodenal tube test; EHBDs, Extrahepatic biliary ducts; ERCP, Endoscopic retrograde cholangiopancreatography; GB, Gallbladder; GGT, Gamma-glutamyl transpeptidase; HAD, Hepatic artery diameter; HLA, Human leukocyte antigen; HUS, High frequency ultrasound; IHBDs, Intra-hepatic biliary ducts; IL, Interleukin; KPE, Kasai portoenterostomy; LKPE, Laparoscopic Kasai portoenerostomy; LT, Liver transplantation; MRCP, Magnetic resonance cholangiopancreatography; NC, Neonatal cholestasis; NPV, Negative predictive value; PPV, Positive predictive value; UDCA, Ursodeoxycholic acid; US, Ultrasound; TC sign, Triangular cord sign.

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## Introduction

Neonatal cholestasis (NC) is a multifaceted diagnostic problem that may be incorrectly diagnosed as physiologic jaundice, thus postponing the management of serious liver diseases that require urgent management. NC can be caused by infections, and drug reactions, in addition to endocrine, metabolic, inflammatory, immunologic, and anatomic disorders of the biliary tree.[1] Biliary atresia (BA) is one of the etiologies of NC and is considered the most fatal pediatric liver disease, therfore, BA should be detected early and properly managed.[2] BA is a rare disease that exclusively affects newborn infants and is characterized by ascending obstruction of the bile ducts with a greater effect on extra-hepatic biliary ducts (EHBDs).[3]

## Epidemiology of BA

BA is more common among females,[4,5] and nonwhite indviduals are more prone to exhibit BA. Full-term infants with low birth weights (<2500 g) are at a higher risk of developing BA than infants born at term with normal birth weights.[6] Familial, clustering of BA is extremely rare, and disease concordance in twins is unusual.[7] Although seasonal clustering of the disease also has been reported,[5] this finding was not supported in a large study conducted in Japan.[8] Multiparty and advanced maternal age may increase the risk of BA.[9]

## Classification of BA

Based on the associated congenital anomalies, BA can be further classified into three categories. First, perinatal atresia that is not associated with other anomalies or malformations, which affects approximately 70% of BA patients who are jaundice free at birth.[10] Second, biliary atresia splenic malformation syndrome (BASM); which is observed in one-tenth of BA patients, and is associated with situs inversus, malrotation, dextrocardia asplenia or polyspleina, an interrupted inferior vena cava and congenital heart disease. BASM has a worse prognosis than does perinatal BA.[11] Third, BA associated with choledochal cysts, kidney anomalies and cardiac defects, accounting for 10–15% of BA the patients.[12]

BA can be further divided into correctable and non-correctable types. The former accounts for 10–15% of cases, in which the proximal common hepatic duct is patent, allowing primary anastomosis of the EHBDs to the bowel. The latter does not exhibit the patency found in correctable BA[13] (Fig. 1).

## Etiology

BA is a phenotype that is considered to result from several pathogenic processes leading to obstruction of the biliary tree.[14]

### *Genetic factors*

Mutation of Jagged (Jag1) gene has been reported in patients with BA. This gene plays an immune-regulatory role, suppressing inflammatory cytokines (IL-8) production.[3] Mutation of a gene belonging to the cryptic family (CFC1) that is thought to act as a cofactor in pathways determining the left-right axis has been also reported in minority of patients with the sporadic form of the disease [15] and BASM.[16] There is a contradiction regarding the association between Human leukocyte antigen (HLA) and BA. Some authors have supported this association,[17] while and others have not.[18] Furthermore, vascular endothelial growth factor gene polymorphism is thought to be involved in BA in an indirect manner by increasing susceptibility to the disease.[7]

A recent theory regarding the development of BA involves somatic mutations occurring after zygote formation that affect only a subset of cells. The phenotypes depend on the time at which the mutation occurs, with earlier occurance potentially causing de novo dominant disease. Later mutations can lead to whole-body mosaicism or can be restricted to a subset of tissues, and the same concept is applicable for BA phenotypes. The success rate of Kasai portoenterostomy (KPE) can be explained by the rate of mosaicism in different parts of the liver.[19]

### *Immunological injury*

This theory is supported by the presence of mononuclear inflammatory infiltrates within damaged IHBDs and the biliary epithelium.[20] The trigger is not known, an initial insult to the