

Review Article

Biliary atresia: a review

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ABSTRACT

Bile duct atresia (BA) is a severe, progressive cholangiopathy characterized by fibrous and inflammatory obliteration of the intrahepatic and extrahepatic bile ducts. It leads to liver failure, scarring, and end-stage cirrhosis if timely treatment is not achieved. It represents the number one indication for pediatric liver transplantation as a single disease worldwide. Various etiological factors have been associated with BA, such as structural malformations, viral, immune-mediated, and genetic infections. The incidence of BA varies around the world. Untreated BA patients have a 2-year mortality of nearly 100%. The clinical picture is characterized by jaundice, acholia, and jaundice that persists beyond the first 2 weeks of life. Direct or conjugated bilirubin remains the primary screening laboratory test for BA; elevated values occur within the first 2 days of life. Currently, the primary treatment of choice is the Kasai portoenterostomy; the success of surgery has been based on the restoration of bile flow and the elimination of jaundice. However, more than 70% of patients develop liver cirrhosis secondary to persistent liver inflammation, which will require liver transplantation. The following review of the literature aims to collect relevant information from what has been published in recent years on bile duct atresia; focused on the study of etiology, pathophysiology, advances in genetics and immunology. As well as the results associated with surgical treatment and the requirement for liver transplantation.

Keywords: Bile duct atresia, Cholestasis, Cholangiopathy, Kasai portoenterostomy, Liver transplantation

INTRODUCTION

Bile duct atresia (BA) is a severe, progressive cholangiopathy of unknown etiology that occurs in infants, characterized by fibrous and inflammatory obliteration of the intrahepatic and extrahepatic bile ducts, resulting in obstruction of bile flow. It leads to liver failure, scarring, and end-stage cirrhosis if timely treatment is not achieved.¹ BA is one of the main causes of neonatal cholestasis and represents the number one indication for pediatric liver transplantation as a unique disease worldwide.² Various etiological factors have been associated with BA,

including structural malformations, viral infections (reovirus type 3, rotavirus, Epstein Barr virus, and cytomegalovirus infection), immune-mediated, and genetic. About 10% of infants with BA have other congenital malformations.^{3,4} Since it was initially suggested by Benjamin Landing in 1974, several studies mention viral infections as the etiology of BA; cytomegalovirus, reovirus, rotavirus, human papillomavirus, Epstein-Barr virus, and human herpes 6 have been demonstrated by serological markers, liver detection, and bile duct remains. 6 It has also been correlated with bacterial infections such as *E. coli*.^{2,5} To

date, no specific alteration in BA has been related during embryogenesis. Malformations in the ductal plate that persist after birth have been proposed as the etiology; secondary to abnormal cell fate of the developing bile duct.⁶ The biliary system develops mainly during the first trimester of pregnancy. During the third to fourth week of gestation, the first outline of the bile ducts and the liver begin to develop, continuing until the eighth week of gestation. The interactions between the epithelium and the mesenchymal tissues allow the development and remodeling of the biliary system, forming a double cell layer that will lead to the formation of the ductal plaque. The ductal plate forms between 11 and 13 weeks of gestation. It is a bilayer tubular structure surrounded by a thick mesenchyme, it consists of portal veins surrounded by hepatic cell precursors, which remodel and form the intrahepatic biliary tree; it extends from the hepatic hilum towards the periphery along the branches of the portal vein. It gradually disappears, except for a focal area where it forms a lumen and gives rise to the intrahepatic bile ducts. Its postnatal persistence raises the possibility that abnormal mesenchymal signals and cholangiocytes arrest bile duct remodeling.⁷ There is a subgroup known as biliary atresia and splenic malformation syndrome (BASM), considered to be the result of the pathological process during the embryological phase of organogenesis. A small percentage of patients with this syndrome have underlying genetic defects. Mutations in several ciliopathy and laterality genes, including cryptic family 1 (CFC1) and PKD1L1, have been suggested as a potential factor for BASM syndrome. Some cases appear to be secondary to an abnormal intrauterine environment, such as gestational diabetes. Patients with this syndrome present splenic malformations in more than 80%, preduodenal portal vein, absent inferior vena cava, malrotation, with or without situs inversus, and cardiac anomalies. Recently, BASM has been reported to be comparable with patients with isolated BA, with overall survival rates and in terms of native liver.⁴

Kotb's disease; a variant of BA, in which an aflatoxin-induced cholangiopathy occurs in glutathione S transferase (GST) M1 deficient neonates born to GST M1 heterozygous mothers; there is a disorder of the genomics of childhood detoxification. Pathophysiology is explained by massive damage to liver tissue by congenital aflatoxicosis causing inflammation, fibrosis, adhesions, bile duct proliferation, scarring, cholestasis, focal syncytial giant cell transformation, and infiltration by CD4+, CD8+, CD68+, CD14+, neutrophil infiltration, neutrophil elastase spillage, heavy aflatoxin B1 loads, accelerated cirrhosis, altered p53 and GSTP1, and glutathione S transferase M1 (GSTM1) null. Typical alteration of both p53 and GSTP1 causes loss of liver regeneration.⁸

EPIDEMIOLOGY

The incidence of BA varies around the world, occurring more frequently in Asia; from 1 in 5000 in Taiwan.

1:10,000 in Japan, 1: 14,000 in Sweden, 1 in 15,000 in the USA to about 1 in 19,000 live births per year in the Netherlands. It has a slight predominance in the female sex (1.25:1), mainly in patients with splenic malformations, the incidence is higher in non-white infants.^{5,9} A predominance of affected infants during the fall (August-October) was reported by Strickland and Shannon.¹⁰ However, subsequent studies in Hawaii, the Netherlands, Michigan, and England did not identify seasonal variation or temporal clustering. Recently, in a study conducted in 119 Japanese infants, reported negligible seasonal and geographic variation in the incidence of BA, underscoring the variable geographic frequency of the disease.¹¹

An association has been found with advanced maternal age, increased parity and a tendency to early fetal loss. Recently, a study was conducted in which mothers with type 2 diabetes and non-dependent drug abuse had higher rates of children with BA with an odds ratio of 2.17 (95% confidence interval [CI] = 1.04 -4.53) and OR: 3.02 (95% CI=1.34–6.78), respectively.¹² It has rare familial recurrence, with twin studies showing most clusters are discordant for the disease.¹³ Untreated BA patients have a 2-year mortality of nearly 100%.¹⁴

PATHOPHYSIOLOGY

The pathophysiology involves inflammation within the walls of the biliary system, a massive immune response, adhesions, and fibrous obliteration of the bile duct. Viral, vascular, and immune toxins such as aflatoxins have been indicated as triggering factors for inflammation of the bile duct wall and BA.² Experimental models of BA and analyzes in human livers have been carried out, where it is suggested that the obstruction and injury of the bile duct is secondary to a type 1 immune response, as well as the proliferation of cholangiocytes in the extrahepatic bile ducts and liver fibrosis promoted by type 2 cytokines (Figure 2).

Mechanisms of epithelial injury and occlusion of bile ducts

After viral infection, macrophages, dendritic cells, and cholangiocytes trigger an autocrine and paracrine antiviral response in both infected and surrounding cells through type I interferons (IFNs) to prevent the virus from spreading. In infected cells, type I IFNs promote biliary apoptosis by upregulating tumor necrosis factor-related apoptosis ligand (TRAIL) (p55 TNF receptor) and CD95 (Fas/Apo1 ligand). In the surrounding tissue, IFNs trigger the production of antiviral proteins that provide protection against viral infection.¹⁵

Pathogenesis of liver fibrosis

Liver fibrosis corresponds to a healing response secondary to chronic liver injury, characterized by excessive accumulation of collagen and extracellular matrix in the liver.¹⁶ In BA, liver fibrosis is characterized by rapidly

progressing, even after successful surgical restoration of bile flow by Kasai portoenterostomy.

So far, the pathogenic factors have not been fully elucidated. However, the hypothesis is that an initial viral insult occurs during the perinatal period, triggering an autoimmune response, resulting in bile duct injury and fibro obliteration. To summarize these mechanisms, the fibrogenic cascade in the liver with BA can be divided into three stages (Table 1 and Figure 2).¹⁷

MOLECULAR BASE AND GENETIC ANALYSIS

Genetic mutations related to biliary atresia are currently an important study target. Since 1993, Yokoyama et al conducted experiments in mice where they identified that the inactivation or overexpression of the *Foxa1*, *Foxa2*, *Foxf1*, *Hes1*, *Hnf6*, *Hnf1b*, *Invs*, *Lgr4*, *Pdx1*, *Sox17* genes and in mice has been shown to alter the normal embryogenesis of the extrahepatic biliary system, causing a spectrum of anatomic malformations of the gallbladder and extrahepatic bile ducts, including hypoplasia and agenesis. For example, *INVS* mutations were not identified in children with laterality defects and biliary atresia.¹⁸

Recently, Zheng et al conducted a study where they reported elevated serum levels and hepatic expression of endothelial growth factor (EGF). Phosphorylated EGF receptor (p-EGFR) and extracellular regulated kinase 1/2 (p-ERK1/2) were increased. Concluding that EGF is overexpressed in BA and aggravates liver fibrosis through the EGF/EGFR-ERK1/2 pathway, which may be a therapeutic target.¹⁹ Cui et al observed a statistically significant increase in deletions at 2q37.3 in patients with ABV, resulting in the deletion of one copy of *GPC1* (regulates inflammation and Hedgehog signaling, encoding glypican 1, a heparan sulfate proteoglycan). Liver samples from ABV patients had reduced levels of apical *GPC1* in cholangiocytes, compared to samples from controls. Concluding that *GPC1* seems to be a BA susceptibility gene. These findings also support a role for Hedgehog signaling in pathogenesis.²⁰ Li et al conducted a study where the *ADD3* rs2501577 polymorphic locus was associated with increased risk of biliary atresia, particularly in Asian populations. Recommending further investigation of the *ADD3* rs2501577 locus in Asian populations to validate its role in the diagnosis of biliary atresia.²¹ Studies investigating gene sequence variants as susceptibility factors for biliary atresia are gaining interest, such as reports of single nucleotide polymorphisms (SNPs) in *JAG1*, *CD14*, *MIF*, *ITGB2*, *ADIPOQ*, and *VEGF*.⁹

CLASSIFICATION

BA can be classified into four clinical forms, the Japan Association of Pediatric Surgeons proposed an anatomical classification of BA depending on the location of the atresia (Tables 2 and 3).^{9,17,22}

DIAGNOSIS

There are syndromic and non-syndromic forms of BA; the non-syndromic form occurs in up to 80% to 90% of patients. The syndromic form is associated with congenital heart disease, polysplenia, heterotaxy, preduodenal portal vein, and inferior vena cava (IVC) anomalies.²³ Clinically, children present acholia, choloria, and jaundice.⁷

ABV is the most common cause of obstructive cholestasis in the newborn, in which infants develop jaundice, acholia, and jaundice that persists beyond the first 2 weeks of life. Direct or conjugated bilirubin remains the primary screening laboratory test for BA; elevated values occur within the first 2 days of life.²⁴ A new biomarker, matrix metalloproteinase-7 (MMP-7), has shown promising results, with >95% sensitivity and specificity for biliary atresia, and could be useful in diagnosis.⁷ In a study by Robie et al, an elevated serum gamma-glutamyl transpeptidase (GGT) level was shown to be strongly associated with biliary atresia; however, by itself it is not diagnostic.²⁵ Abdominal ultrasound makes it possible to identify anatomical alterations that cause obstructive cholestasis, as well as visualize data that correlates with the diagnosis of BA, such as abnormal gallbladder, absent common bile duct, vascular abnormalities such as preduodenal portal vein, polysplenia, asplenia, and triangular cord sign.²⁶ Once a high index of suspicion is established, the intraoperative cholangiogram (IOC) is performed, it is considered positive if the patent extrahepatic bile duct is not visualized. Subsequently, Kasai portoenterostomy (KPE) is performed as the primary treatment to promote biliary drainage. IOC combined with KPE also helps define the specific anatomic variant, which may have prognostic implications (Figure 1).²⁴

HISTOPATHOLOGICAL STUDY

At the tissue level, the intrahepatic bile ducts are usually hyperplastic, with variable degrees of fibrosis, surrounded by lobules with characteristics of cholestasis and giant multinucleated hepatocytes. In the extrahepatic bile ducts, there is segmental or general loss of the epithelial lining, with extensive fibrosis and foci of inflammation.⁹ Characteristics that potentially correlate with outcome have been identified in the histopathological study of the liver in patients with BA (Table 4).

TREATMENT

Currently, the primary treatment of choice is the Kasai portoenterostomy, which was introduced in 1959 with the aim of restoring bile flow. The success of surgery has been based on the restoration of bile flow and the elimination of jaundice. However, more than 70% of Kasai patients develop cirrhosis secondary to persistent liver inflammation.¹⁴ The initial surgical management is the excision of the entire area of the obliterated biliary tree, incising at the level of the porta hepatis to expose the

microscopic but functional bile ducts. Subsequently, diversion surgery is performed by creating a Roux-en-Y loop from the proximal jejunum and anastomoses to the cut surface (Kasai portoenterostomy). Restoring bile flow. Without having a parameter to measure bile flow; Elimination of jaundice and normal bilirubin values are considered within a set period of 6 months after the procedure, which was achieved in approximately 57% of cases.²⁷ There are factors that influence the success of the surgical procedure (Table 5).²⁸ Regarding post-surgical treatment, what is reported in the bibliography is intravenous antibiotic therapy and subsequently low-dose prophylactic oral antibiotics, which can be cycled at intervals of 8 or 12 weeks (for example, amoxicillin 125 mg per day, cephalexin 125 mg per day, trimethoprim 120 mg per day) for a minimum of 12 months ursodeoxycholic acid, as well as fat-soluble vitamin formulations which are

essential for preventing malnutrition, overcoming fat malabsorption, and reducing the effect of excessive catabolism should include vitamin A 5–15,000 IU per day, vitamin D 50 ng/kg/day, vitamin E 50–200 mg per day, and vitamin K 2.5–5 mg per day. If the patient has steatorrhea due to fat malabsorption, it can be controlled by providing between 40% and 60% of the fat in the food as medium chain triglycerides.^{15,28} Steroid use has been reported. However, in the START trial, it was observed that administration of corticosteroids within 3 days after Kasai portoenterostomy did not change the outcome of BA, and increased the risk of serious adverse effects compared with placebo controls.¹⁵ The role of immunomodulatory therapies such as immunoglobulins, steroids, colchicine; It is controversial, however it has been suggested as an adjunct to surgical treatment.²



Figure 1: Morphological classification of bile duct atresia (A) type I, obliteration of the common bile duct, (B) type IIa, obliteration of the common hepatic duct, (C) type IIb obliteration of the common hepatic, bile duct, and cystic ducts, and (D) type III, intra and extra hepatic bile duct obliteration.

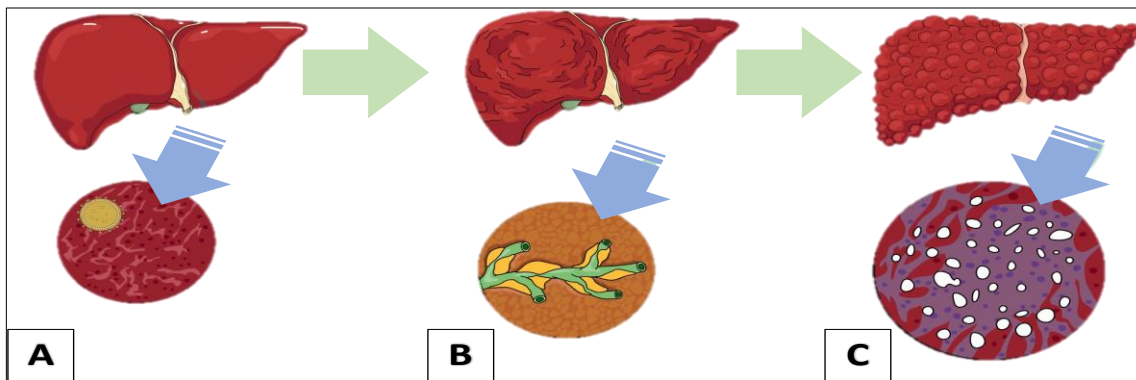


Figure 2: Pathophysiology of bile duct atresia (A) hepatic inflammation due to a pathogenic factor (pathogenic factors involved; alteration in morphogenesis, genetic factors, alterations in embryogenesis, abnormal prenatal circulation, immunological dysregulation, susceptibility factors, autoimmunity, abnormal inflammatory response, environmental factors, viruses, toxins), (B) hepatic fibrosis, and fibrous obliteration of the bile duct; hepatic fibrogenic cascade: inflammatory lesion of the liver, activation of myofibroblasts, formation of fibrous scar, and (C) cirrhosis of the liver.

Table 1: Fibrogenic cascade in the liver with bile duct atresia.

Stage	Characteristics	Mechanism
First stage	Inflammatory liver lesion	Caused by persistent inflammation and immune response
Second stage	Activation of myofibroblasts	Increases the number of myofibroblasts from activated hepatic stellate cells, portal fibroblasts, and biliary epithelial-mesenchymal transition
Third stage	Formation of a fibrous scar	Accumulation of collagen secreted by fibrogenic myofibroblasts resulting in the formation of a fibrous scar in the liver, which can progress to cirrhosis

Table 2: Classification of clinical forms of bile duct atresia.

Type	Incidence	Characteristics	Pathogenesis	Associated malformations
Embryonic BA	10-15%	Early onset of bile duct injury. Extrahepatic bile ducts may be absent Jaundice at birth	Genetic mutations	Splenic malformations in 8-12%
Cystic BA	5-10%	Presence of cystic malformation adjacent to the site of common bile duct obstruction. Prenatal diagnosis can be made during routine ultrasound, Jaundice and acholia may present shortly after birth or 1 to 3 months of life	Type 2 cytokine response, TH2 prominent in mouse models of rotavirus-induced biliary atresia	Some infants share features of BASM
BA associated with CMV	10%	DNA and/or protein of cytomegalovirus in liver	CMV infection	None
Perinatal or non-syndromic BA	70-80%	Apparently healthy infant, develops cholestatic symptoms after the first weeks of life	Type 1 cytokine response	They can present malformations cardiovascular and intestinal malrotation

Table 3: Anatomical classification of BA.

Type	Level	Percentage of cases
Type I	Common bile duct obliteration	12
Type II	IIa. Common hepatic duct obliteration IIb. Obliteration of the hepatic, cystic, and common bile ducts	2.5
Type III	Obliteration of the common, hepatic, and cystic ducts without anastomosable ducts in porta hepatis	About 85

Table 4: Histopathology characteristics in BA.

Characteristic	Definition
Ductal plaque malformation	Intrahepatic bile ducts retaining the fetal configuration. suggests that the disease involves abnormal development of the intrahepatic bile ducts beginning in the prenatal period
Ductular reaction	Injury-induced proliferation of reactive bile ducts in the liver. Persistent injury to the biliary epithelium induces the inflammatory reaction and activates the biliary repair complex called the ductular reaction, resulting in excessive collagen production around the damaged bile ducts
Portal tract inflammation	Infiltration of inflammatory cells into the portal tract. These inflammatory cells infiltrating the portal space are composed of lymphocytes, CD4+ T cells, CD8+ T cells, macrophages, and natural killer (NK) cells
Liver fibrosis grade	It is assessed and scored by the change in fibrous architecture and expansion of fibrotic areas between the portal spaces [58, 59] or by collagen staining in the liver. Myofibroblast (α -smooth muscle actin) expression in liver BA has been reported to be related to the degree of liver fibrosis

Table 5: Factors that influence the success of the surgical procedure.

S. no.	Factors that influence the success of the surgical procedure
1	Age at time of surgery
	Elimination of jaundice and preservation of the native liver has been associated with early portoenteroanastomosis
2	Histology
	It has been established that the histopathological findings and the extrahepatic biliary remnant have an influence in the long term; those patients with small bile ducts in the transected remnant will have worse bile flow
3	Surgical experience
	Experience has been shown to be directly proportional to short- and long-term results. Therefore, currently the world trend is to refer to certain centers that frequently treat this pathology

Commonly reported adverse prognostic factors are late Kasai surgery (more than 2-3 months of age), intrahepatic panbiliary disease, and the presence of the syndromic form of BA. Regarding the histopathological characteristics that have been related to the result, they are extension of histological or molecular fibrosis, liver inflammation, and bile duct proliferation; the presence of malformation of the ductal plate; and the presence of large bile ducts in the porta hepatis, defined as ducts with a lumen diameter greater than $\geq 150 \mu\text{m}$.¹⁴ BA is the most frequent indication for liver transplantation in pediatric patients. Some centers opt for the Kasai procedure in the first instance and thus delay the transplantation, compared to other centers that do not prefer it since it can form multiple adhesions and complicate liver transplantation in a second surgical stage. Indications for transplantation include cirrhosis, liver failure, gastrointestinal bleeding from portal hypertension, pruritus, and recurrent episodes of cholangitis. It has been observed that performing the Kasai procedure for a subsequent liver transplantation in patients with liver failure presents greater survival; however, when the Kasai portoenterostomy fails, mortality after liver transplantation increases.⁷

DISCUSSION

The pathophysiology of BA continues to be a target of study; Various studies on genetic and immunological correlation have recently been published, opening doors for possible therapeutic targets. Lin et al, identified an association of SNP rs1518111 in interleukin 10 (IL10) BA ($p=5.79\text{E-}03$; OR: 0.80; 95% CI: 0.68–0.94). As well as epistatic effects of the following pairwise interactions between these single nucleotide polymorphisms: signal transducer and activator of transcription 4 (STAT4) and chemokine (C-X-C motif) ligand 3 (CXCL3); STAT4 and damage regulated autophagy modulator 1 (DRAM1); CXCL3 and RAD51 paralog B (RAD51B); and interferon gamma (IFNG) and interleukin 26 (IL26). In addition, IL-10 effectively prevented biliary epithelial cell injury and biliary obstruction in murine BA, and inhibition of BA-related immune cell activation.²⁹ In a study by Kotb et al where they conducted a 10-year retrospective analysis, found that of the 779 infants with cholestasis, 61 (7.8%) had Down syndrome. They followed up for a mean duration $\pm\text{SD} = 12.1\pm 16.7$ months, reporting that none presented extrahepatic bile duct atresia; therefore, it seems that there are genetic protectors against BA that remain to be explored.³⁰ Various prognostic histological factors have been described. Nguyen AP, Pham YHT performed a retrospective review of liver histologies in BA patients operated on with the Kasai technique in order to identify histological prognostic factors for biliary outcome. Where they observed that total bilirubin levels $>34 \mu\text{M}$ correlate with worse 1-year survival. Potential adverse predictors being severe hepatocellular inflammation, severe cholestasis, presence of ductal plate malformation, and portal plate bile duct size $<150 \mu\text{m}$ ($n=28$).

Histologic findings of bile duct portal plaque size $<150 \mu\text{m}$ and severe hepatocellular damage predict poor post-Kasai surgery jaundice clearance, with short-term survival outcome, regardless of timing. kasai surgery.¹⁴ Liliemark et al carried out a retrospective study, where 15 of 46 (33%) patients diagnosed with BA presented signs of ongoing CMV infection. They did not differ significantly from CMV-negative patients in terms of birth weight, prematurity rate, or biochemical markers, however age at Kasai portoenterostomy was higher. All patients received steroids after surgery; all patients with ongoing CMV infection received antiviral treatment with adequate control of viraemia and no major side effects. Antiviral treatment consisted of oral valganciclovir (10-40 mg/kg/d) or intravenous ganciclovir (5.3-11 mg/kg/d).⁵ Hoshino performed a meta-analysis that demonstrated the importance of early diagnosis and surgical interventions before 30 days of life in patients with BA on native liver survival at 5, 10, and 20 years. Hazard ratios meta-analysis revealed that there was a significantly faster time to liver transplantation in the group of patients who had PEK after 30 days compared with prior PEK (HR=2.12, CI 95%: 1.51–2.97).³¹

CONCLUSION

Bile duct atresia is a serious pathology that affects newborns and infants. Due to its rapid progression to liver cirrhosis, and the prognosis associated with age at the time of surgery; early suspicion and diagnostic approach is of vital importance to provide timely treatment and thus improve the prognosis and survival of patients. Since the etiology is not yet precise, it represents a diagnostic challenge. However, currently, various fields of research have been opened on the genetics and immunology of the pathology that offer possible therapeutic targets. Kasai portoenterostomy represents the primary surgery, however follow-up is important, since up to 70% of patients will develop liver cirrhosis secondary to persistent inflammation, requiring liver transplantation.

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REFERENCES

1. Tran KT, Le VS, Dao LTM, Nguyen HK, Mai AK, Nguyen HT, et al. Novel findings from family-based exome sequencing for children with biliary atresia. *Sci Rep*. 2021;11(1):21815.
2. Kotb MA, Ieiri S, Shehata SM. Editorial: Elimination of biliary atresia. *Front Pediatr*. 2023;11:1202727.
3. Petersen C, Madadi-Sanjani O. Role of viruses in biliary atresia: news from mice and men. *Innovative Surg Sci*. 2018;3:101-6.
4. Xu X, Dou R, Zhao S, Zhao J, Gou Q, Wang L, et al. Outcomes of biliary atresia splenic malformation (BASM) syndrome following Kasai operation: a

- systematic review and meta-analysis. *World J Pediatr Surg.* 2022;5(3):e000346.
5. Liliemark U, Svensson JF, Fischler B. Incidence and antiviral treatment of cytomegalovirus infection in infants with biliary atresia. *Pediatr Surg Int.* 2023;39(1):117.
 6. Desmet VJ. Congenital diseases of intrahepatic bile ducts: variations on the theme "ductal plate malformation". *Hepatology.* 1992;16(4):1069-83.
 7. Brahee DD, Lampl BS. Neonatal diagnosis of biliary atresia: a practical review and update. *Pediatr Radiol.* 2022;52(4):685-92.
 8. Kotb MA, Kotb A, Talaat S, Shehata SM, El Dessouki N, ElHaddad AA, et al. Congenital aflatoxicosis, mal-detoxification genomics & ontogeny trigger immune-mediated Kotb disease biliary atresia variant: SANRA compliant review. *Medicine (Baltimore).* 2022;101(39):e30368.
 9. Asai A, Miethke A, Bezerra JA. Pathogenesis of biliary atresia: defining biology to understand clinical phenotypes. *Nat Rev Gastroenterol Hepatol.* 2015;12(6):342-52.
 10. Strickland AD, Shannon K. Studies in the etiology of extrahepatic biliary atresia: time-space clustering. *J Pediatr.* 1982;100:749-75.
 11. Wada H, Muraji T, Yokoi A, Okamoto T, Sato S, Takamizawa S, et al. Insignificant seasonal and geographical variation in incidence of biliary atresia in Japan: a regional survey of over 20 years. *J Pediatr Surg.* 2007;42(12):2090-2.
 12. Chang CM, Kuo KC, Chen WH, Su CH, Lee CP, Chen KJ, et al. Maternal risk factors associated with offspring biliary atresia: population-based study. *Pediatr Res.* 2023;93(4):1064-71.
 13. Fallon SC, Chang S, Finegold MJ, Karpen SJ, Brandt ML. Discordant presentation of biliary atresia in premature monozygotic twins. *J Pediatr Gastroenterol Nutr.* 2013;57(4):e22-3.
 14. Nguyen AP, Pham YHT, Vu GH, Nguyen MH, Hoang TN, Holterman A. Biliary atresia liver histopathological determinants of early post-Kasai outcome. *J Pediatr Surg.* 2021;56(7):1169-73.
 15. Ortiz-Perez A, Donnelly B, Temple H, Tiao G, Bansal R, Mohanty SK. Innate Immunity and Pathogenesis of Biliary Atresia. *Front Immunol.* 2020;11:329.
 16. Parola M, Pinzani M. Liver fibrosis: pathophysiology, pathogenetic targets and clinical issues. *Mol Aspects Med.* 2019;65:37-55.
 17. Chusilp S, Balsamo F, Li B, Vejchapitap P, Pierro A. Development of liver inflammatory injury in biliary atresia: from basic to clinical research. *Pediatr Surg Int.* 2023;39(1):207.
 18. Yokoyama T, Copeland NG, Jenkins NA, Montgomery CA, Elder FF, Overbeek PA. Reversal of left-right asymmetry: a situs inversus mutation. *Science.* 1993;260(5108):679-82.
 19. Zheng Q, Li M, Chen L, Zhang C, Zhao Y, Liu G, et al. Potential therapeutic target of EGF on bile duct ligation model and biliary atresia children. *Pediatr Res.* 2023.
 20. Cui S, Leyva-Vega M, Tsai EA, EauClaire SF, Glessner JT, Hakonarson H, et al. Evidence from human and zebrafish that GPC1 is a biliary atresia susceptibility gene. *Gastroenterology.* 2013;144(5):1107-15.
 21. Li TF, Ke XY, Zhang YR, Zhan JH. The correlation between rs2501577 gene polymorphism and biliary atresia: a systematic review and meta-analysis. *Pediatr Surg Int.* 2023;39(1):206.
 22. Ibrahim M, Miyano T, Ohi R, Saeki M, Shiraki K, Tanaka K, et al. Japanese Biliary Atresia Registry, 1989 to 1994. *Tohoku J Exp Med.* 1997;181(1):85-95.
 23. Napolitano M, Franchi-Abella S, Damasio MB, Augdal TA, Avni FE, Bruno C, et al. Practical approach to imaging diagnosis of biliary atresia, Part 1: prenatal ultrasound and magnetic resonance imaging, and postnatal ultrasound. *Pediatr Radiol.* 2021;51(2):314-31.
 24. Antala S, Taylor SA. Biliary Atresia in Children: Update on Disease Mechanism, Therapies, and Patient Outcomes. *Clin Liver Dis.* 2022;26(3):341-54.
 25. Robie DK, Overfelt SR, Xie L. Differentiating biliary atresia from other causes of cholestatic jaundice. *Am Surg.* 2014;80(9):827-31.
 26. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2017;64(1):154-68.
 27. Davenport M, De Ville de Goyet J, Stringer MD, Mieli-Vergani G, Kelly DA, et al. Seamless management of biliary atresia in England and Wales (1999-2002). *Lancet.* 2004;363(9418):1354-7.
 28. Kelly DA, Davenport M. Current management of biliary atresia. *Arch Dis Child.* 2007;92(12):1132-5.
 29. Lin Z, Tian Y, Chai C, Fu M, Wu Q, Tan L, et al. The association of immune-related genes and the potential role of IL10 with biliary atresia. *Pediatr Res.* 2023.
 30. Kotb MA, Draz I, Basanti CW, El Sorogy ST, Abd Elkader HM, Esmat H, et al. Cholestasis In Infants With Down Syndrome Is Not Due To Extrahepatic Biliary Atresia: A Ten-Year Single Egyptian Centre Experience. *Clin Exp Gastroenterol.* 2019;12:401-8.
 31. Hoshino E, Muto Y, Sakai K, Shimohata N, Urayama KY, Suzuki M. Age at surgery and native liver survival in biliary atresia: a systematic review and meta-analysis. *Eur J Pediatr.* 2023;182(6):2693-704.

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