# Congenital extrahepatic biliary atresia in children in Slovenia – epidemiological retrospective data

## Prirojena atrezija zunajjetrnih žolčevodov pri otrocih iz Slovenije – epidemiološki retrospektivni podatki

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## Izvleček

**Izhodišča:** Cilj te raziskave je bil ugotoviti anamnestične in klinične značilnosti, izvide laboratorijskih in slikovnih preiskav ter izid zdravljenja otrok, ki se rodijo z atrezijo zunajjetrnih žolčevodov v Sloveniji.

**Metode:** V epidemiološki retrospektivni raziskavi smo zbrali medicinsko dokumentacijo otrok, rojenih v Sloveniji med oktobrom 1996 in oktobrom 2011, ki smo jim na Pediatrični kliniki Univerzitetnega kliničnega centra v Ljubljani postavili diagnozo atrezija žolčevodov. Raziskovali smo epidemiološke podatke in izid zdravljenja bolnikov z atrezijo žolčevodov v Sloveniji.

**Rezultati:** V obdobju 15 let smo atrezijo žolčevodov potrdili pri 16 otrocih (1/20000 novorojenčkov). Dve tretjini bolnikov v naši skupini je bilo deklic. En otrok je imel pridruženo nepravilno lego notranjih organov. Večina bolnikov se je rodila v jesenskih in zimskih mesecih. Oboleli novorojenčki so se rodili donošeni s primernimi porodnimi merami in zdravi, vendar je večina od njih postala zlatenična v prvih dneh življenja. Primarno operacijo so opravili pri 11 otrocih pri srednji starosti 70 dni. Trinajstim otrokom (81 %), pri katerih operacija ni bila uspešna, so jetra presadili v kirurških centrih zunaj Slovenije. Srednja starost pri presaditvi jeter je bila 9 mesecev, srednji čas od operacije po Kasaiu do presaditve jeter pa 5 mesecev. Srednji čas sledenja je bil 9,75 leta (razpon 1,2–15,4).

**Zaključki:** V Sloveniji je pojavnost atrezije žolčevodov nizka in pojavnost atrezije žolčevodov z malformacijo vranice zelo redka. Sezonsko pojavljanje, ki se opaža, bi lahko nakazovalo virusno etiologijo.

## Abstract

**Background:** The objective of this study was to investigate the history, clinical, laboratory, imaging data and outcome of children with biliary atresia in Slovenia.

**Methods:** In an epidemiological single-arm retrospective study health records of infants born in Slovenia between October 1996 and October 2011, who were diagnosed with biliary atresia at the University Children's Hospital, University Medical Centre Ljubljana, were reviewed. Epidemiological data and outcomes of patients with biliary atresia in Slovenia were studied.

**Results:** In the 15-year period, 16 cases of biliary atresia were confirmed (1/20000 newborns). Two thirds of patients in our cohort were females. One child had associated laterality malformation. The majority of patients were born in autumn and winter months. The affected newborns were born mature with appropriate birth measures and healthy, but most of them became jaundiced in the first days of life. Primary surgery was done in 11 children at median age of 70 days. Of those children in whom the surgery was unsuccessful, 13 (81 %) underwent liver transplantation in foreign surgical centres. Median age at liver transplantation was 9 months, median time from Kasai operation to liver transplantation was 5 months. Median follow-up was 9.75 years (range 1.2–15.4).

**Conclusions:** In Slovenia, the incidence of biliary atresia is low and biliary atresia splenic malformation very rare. The observed seasonal incidence might suggest the viral aetiology.

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## Introduction

Extrahepatic biliary atresia (BA) is an idiopathic destructive inflammatory obliterative disease, which affects the extrahepatic biliary ducts. It is a progressive disease that is presented in the neonatal or early postneonatal period with obstruction of the bile flow from the liver. BA is a rare disease detected in about one in 10,000 to 20,000 live newborns. It is the most common cause of neonatal conjugated hyperbilirubinemia where palliative surgery is needed, and also the most common reason for liver transplantation in children.[1-5]

The aetiology of BA is unknown. It still remains to be explained whether the changes in the liver are due to extrahepatic bile duct injury or if the disease primarily affects the liver as well. Among possible explanations of pathogenesis are: the disrupted morphogenesis of biliary ducts, the impeded vascularisation of the biliary ducts before birth and the injury of the bile ducts by viruses, toxins or immunologic abnormalities.[6-8] Regarding genetic aetiologies, there are reports on mutations in the CFC1 gene, encoding a cryptic protein that is involved in determining laterality during foetal development.[9] Anyhow, genetic factors may affect the susceptibility for the disease.[10,11] The aetiology of the disease is probably multifactorial, which is a consequence of genetic and environmental factors.

In Slovenia, newborns with suspicion of BA are referred to the University Children's Hospital of the University Medical Centre, where the diagnostic procedures and the treatment of the disease are managed. Our aim is to report on epidemiological data and outcomes of patients with BA in Slovenia.

## Patients and methods

The medical records of patients who are being followed in the Centre before and after liver transplantation of the Department of Gastroenterology, Hepatology and Nutrition of the University Children's Hospital, University Medical Centre Ljubljana, were analysed retrospectively, and the patients with BA born between October 1996 and October 2011 were reviewed. Data on pregnancy and labour, birth measures, gender, ethnicity, time of onset of jaundice, laboratory, serologic and imaging studies results were reviewed. In addition, liver histology, presence of congenital malformations, time of Kasai operation, type of liver transplantation, postoperative medications and final outcome in terms of complications and growth were also studied. All statistical analyses were done with Statistica for Windows (version 14.0.1, SPSS Inc., Chicago, IL, USA).

In a newborn with suspected BA the series of serologic, laboratory, urine and imaging studies were performed. Clinical characteristics of newborns with BA included jaundice, acholic stools and dark urine. Laboratory testing revealed conjugated hyperbilirubinemia, moderately elevated serum aminotransferases, highly elevated gamma glukuronyl transferase and alkaline phosphatase. Other possible anatomical reasons for biliary obstruction, such as choledochal cyst, were excluded by ultrasound. In newborns with BA, the gallbladder was

**Table 1:** Prevalence of biliary atresia in Slovene regions according to the number of inhabitants.

| Slovene regions | Number of patients | Number of inhabitants | Prevalence of biliary atresia |
|---|---|---|---|
| Gorenjska | 10 | 695 017 | 1:69 502 |
| Dolenjska | 3 | 139 095 | 1:46 365 |
| Štajerska and Koroška | 1 | 765 078 | 1:765 078 |
| Primorska | 1 | 224 651 | 1:224 651 |
| Notranjska | 0 | 51 032 | |
| Prekmurje | 0 | 122 717 | |

either missing, irregular in shape or smaller than usual, with the 'triangular cord' sign or absence of the common bile duct detected by ultrasound. The patency of biliary ducts was detected by HIDA scan after stimulation with phenobarbiton. We excluded intrahepatic biliary hypoplasia by liver biopsy. Biopsy findings in the case of extrahepatic BA showed expanded portal tracts with bile duct proliferation, oedema, fibrosis, inflammation and canalicular and bile duct bile plugs. When in a patient a diagnosis of BA was suspected, the surgeon made laparoscopy and intraoperative cholangiogram. If biliary obstruction was demonstrated, a hepatoportoenterostomy or Kasai operation was done, which was available for every child during this period. When Kasai operation was successful, bile drained into a bowel loop and jaundice disappeared in a few weeks. Patients with unsuccessful Kasai operation and progressive liver disease were referred to foreign medical centres for liver transplantation. Medical costs were covered by the national medical insurance.

## Results

In the 15-year period a total of 16 Slovene children with BA were identified, 10 females (62.5 %) and 6 males (37.5 %). One child had associated laterality malformation, namely situs inversus of internal organs. The majority of patients were born in autumn and winter months (15/16). In terms of the regional origin, 11 children came from Gorenjska, 3 from Dolenjska, one from Štajerska and one from Primorska region (Table 1). Parents of two children came from abroad: one parent originated from Bosnia and Herzegovina and another from China. During pregnancy, 2 mothers had an infection, one had thrombocytopenia.

### Patients'clinical characteristics and evaluation

The majority of children with BA were mature except for one female who was born premature, in the 36$^{th}$ week of gestation. In addition, all patients had appropriate Apgar scores in the first and fifth minute after birth and appropriate birth measures for gestational age (mean birth weight 3270 g (2490–4030 g), mean birth length 50 cm (44–54 cm), mean head circumference 34 cm (32–36 cm)). Two patients were born as twins with only one of the twins affected. Seven children were born as the first child in the family, 4 as the second, 2 as the third and one as the seventh. Three mothers had had previous abortions, one had threatening preterm labour in the affected pregnancy. The labour was vaginal in all the cases except for the twins who were born with caesarean section.

**Table 2:** Liver function tests at referral.

| | Average concentration at presentation | SD (range) | Normal range for term neonates > 5days |
|---|---|---|---|
| Total bilirubin (umol/L) | 194.5 | 78.1 (85–373) | < 171 |
| Conjugated bilirubin (umol/L) | 96.4 | 25.2 (67–146) | 0–3.4 |
| Gamma glutamyl transferase (ukat/L) | 10.1 | 7.7 (1.6–29.2) | 0.25–2.2 |
| Alkaline phosphatase (ukat/L) | 12.9 | 8.6 (4.6–27.5) | 0.8–6.78 |
| Albumin (g/L) | 38 | 2.7 (34–42) | 27–41 |
| INR | 0.78 | 0.26 (0.36–1.2) | 0.53–1.26 |
| Partial thromboplastin time (s) | 42.8 | 13.9 (28–83) | 32–55.2 |

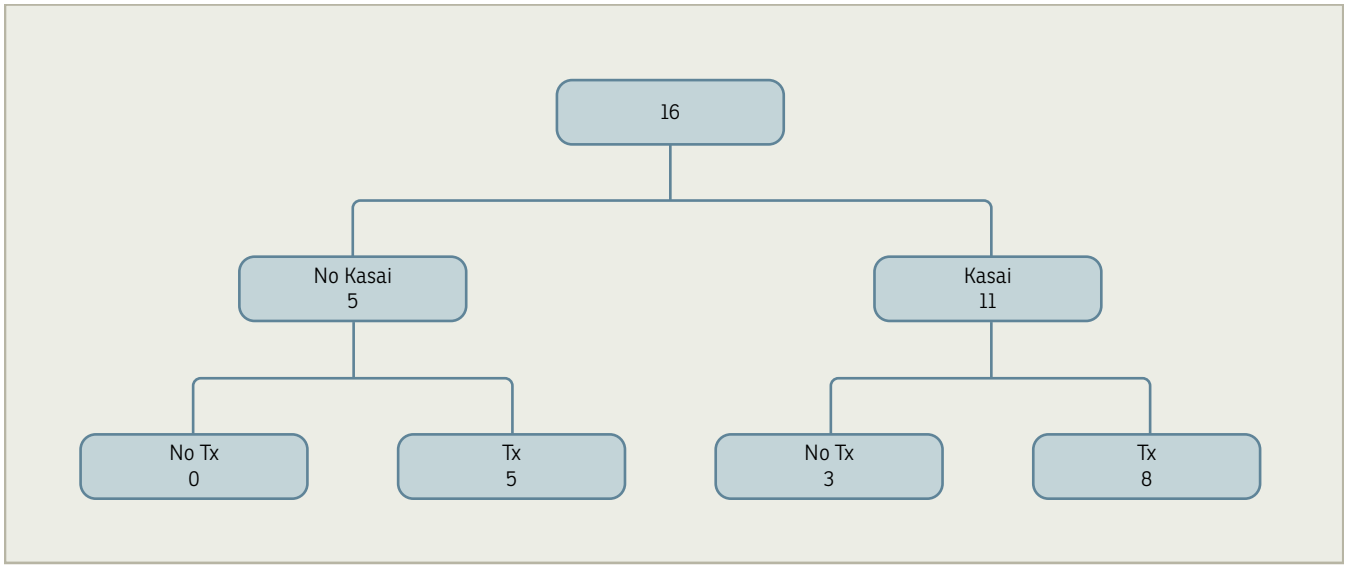


**Figure 1:** Interventions of patient management and outcomes of all biliary atresia study patients. Tx stands for liver transplantation.

The first sign of BA was jaundice, which was visible from birth in 6/16 newborns, in the first 4 days in 6/16 newborns and at the age of one month in the rest. Acholic stools occurred in the first month in 9/16 cases and in the second month in the rest of the cohort.

The mean values, standard deviations, ranges and normal values of biochemical variables in patients with biliary atresia at referral–total and conjugated bilirubin, gamma glutamyl transferase, alkaline phosphatase, albumin and prothrombin time–are shown in Table 2.

The diagnostic evaluation included abdominal sonography and hepatobiliary scintigraphy in all cases, and perioperative liver biopsy in 13/16 cases. By abdominal ultrasound in 12/16 cases the gallbladder was either small or shrinked, in 2/16 cases the gallbladder was missing, and in 2/16 cases this data was not available. In all patients hepatobiliary scintigraphy showed no tracer excretion from the liver to the bowel. Liver biopsy findings showed giant-cell hepatitis, signs of fibrosis, cirrhosis, canalicular and bile duct bile plugs.

## Medical management of the patients

Hepatic portoenterostomy was performed in 11/16 infants with BA, in the rest the operation was either not feasible or the parents did not approve of it. The medical management and survival outcomes of the patients are summarized in Table 3 and Figure 1. After Kasai operation, 3/11 infants had ascending cholangitis. One of the infants had dehiscence with abdominal organs prolapsed, one had duodenal haemorrhage.

In total 13/16 patients with BA underwent liver transplantation in foreign centres (one patient in Hamburg, 12 in Bergamo). Median age at liver transplantation was 9 months (3.5–16 months), median time from Kasai operation to liver transplantation was 5 months (1.5–9 months). Regarding the type of transplantation, in 11 cases they performed split liver transplantation, in 1 case whole liver transplantation and in 1 case the mother donated part of the liver to her child. After the transplantation, children were treated with steroids and tacrolimus in 11 cases and cyclosporine in 2 cases.

Synthetic liver function as regards testing of coagulation, plasma cholinesterase and serum albumin concentration of all children after liver transplantation was within normal limits. Mental and motor development as assessed by patients and their parents was comparable to the normative group. Additionally, in terms of somatic growth 11/16 patients had their weight and height in the range of $10^{th}$–$90^{th}$ percentile for their age and gender, only 1/16 had its weight and height under the $5^{th}$ percentile for his age and gender; all data were gathered 1 year after the liver transplantation. Median follow-up was 9.75 years (range 1.2–15.4).

## Discussion

In the last 15 years we identified and treated 16 patients with BA at the University Children's Hospital, University Medical Centre Ljubljana. According to the data gathered by the Statistical Office of Slovenia, there were on average 20,000 live births per year in the last 15 years in Slovenia. So, the estimated rate of BA in Slovenia would be about 1 in 20,000 live newborns, which is among the lowest rates reported.[1-5] From other southern parts of Central Europe, Croatia also reported a rather low incidence of the disease.[12] Regarding the regional occurrence, the disease is most common in East Asian countries with a reported incidence in Taiwan of 1 in 5000.[13] Also, in our group of patients, the last patient identified was a Chinese girl. In respect of regional occurrence of biliary atresia in Slovenia according to the number of inhabitants, we estimated the highest prevalence of the disease in Dolenjska and Gorenjska region (Table 1). Two thirds of patients in our cohort were females, which is also the case in the Canadian reports.[14]

According to associated congenital malformations, it appears there are three clinical phenotypes of BA. In about 70 % BA occurs without any other anomalies or malformation; this pattern is also referred to as a perinatal BA. Usually these children are born without jaundice, which occurs in the first two months after birth.[4,15] The second phenotype of BA is represented by newborns with associated laterality malformations and is also known as Biliary Atresia Splenic Malformation – BASM or embryonal BA. It occurs in the remaining 10–15 % of newborns with BA. The laterality malformations include situs inversus, asplenia or polysplenia, malrotation of the bowel, interrupted inferior vena cava and cardiac anomalies. Newborns with BASM have normal liver structure at birth with affected extrahepatic biliary ducts.[16] Children with BASM phenotype have worse outcomes compared to newborns with perinatal BA.[15,17] There was only one patient with associated laterality malformation among our patients, which is two times less than in the literature. The girl with BASM is four years old now and is in perfect shape with transplanted liver. The third phenotype is BA in association with other congenital malformations (choledochal cyst, kidney anomalies).

The majority of patients from Slovenia were born in autumn and winter months, which is partially in accordance with other epidemiological studies.[5,18] In New York State they noticed a seasonal pattern of occurrence of BA, with spring births at highest risk in New York City and autumn births in the other parts of New York State. Also, consistent with the infectious disease hypothesis, they found an association of BA with preterm birth and low birth weight, which was not the case in our study. Although BA was not consistently associated with any virus, there are some studies that might support a viral aetiology of the disease.[19]

Besides, the clinical and laboratory characteristics in our group of patients were

**Table 3:** Summary measures and outcomes.

| Variable | |
|---|---|
| Median age at Kasai operation (days) | 70 (30–90) |
| Percentage that underwent Kasai operation | 69 % (11/16) |
| Mean total serum bilirubin level three months after Kasai operation (umol/L) | 193 (21–317) |
| Mean conjugated serum bilirubin level three months after Kasai operation (umol/L) | 107 (9–219) |
| Median age at transplantation (months) | 9 (3.5–16) |
| Median age at transplantation post-Kasai operation (months) | 7 (3.5–12) |
| Median age at referral to transplantation (months) | 9 (6–16) |
| Five-year overall patient survival | 100 % |

typical for BA.[1,3] There was a rise in total and conjugated bilirubin, gamma glutamyl transferase and alkaline phosphatase. Jaundice occurred by the end of the first and acholic stools by the end of the second month of life. Most of the children were jaundiced in the first four days of life and they required phototherapy. On the other hand, only around 2 % of healthy neonatal population needs phototherapy for jaundice. [20] The high incidence of phototherapy use for neonatal jaundice in patients with BA has been already reported previously. [21] Jaundice is a sign of poor biliary flow and can be an indicator of early bile ducts damage already in the prenatal period.

Comparing the time of performing the Kasai operation with other centres, all the operations in our group of patients were performed before the 90$^{th}$ day of life, which is reported to be among most important factors that affect the success of portoenterostomy.[14,22] Yet other reports suggest a clear advantage for the newborns operated on even earlier than 30 days of age.[1,23] Probably with increasing age the liver damage increases and the success is better if the procedure is performed earlier. In our study population the median time from Kasai operation to liver transplantation was 5 months and the median age of liver transplantation was 9 months, which is less than in other reports.[15] As follows, the success of portoenterostomy in our cohort of patients is below 30 %. Among factors that influence the ultimate success of portoenterostomy are also surgeon's experience, patency of the intrahepatic ducts and possibly the postoperative medical management with antibiotics, choleretics[24], and high-dose glukocorticoids.[25-30] The most common complication after the procedure in our cohort was ascending cholangitis, as observed by others.[22] Likewise, the majority of our patients with BA eventually needed liver transplantation because of unsuccessful Kasai operation, which led to portal hypertension and liver failure. Nowadays it is reported that a half of patients require liver transplantation by the end of their second year of life.[31]

In our cohort, there were three surgeons performing the Kasai operation and the last two patients were treated with the suggested glukocorticoid protocol. There are different schemes of postoperative medical management to prevent cholangitis after Kasai operation, but the clear effect of different clinical practices on the outcome is yet to be shown.[15] Although, according to our rather limited experience the use of "anti cholangitis cocktail" improved the outcome of the Kasai operation. Moreover, it was also found that low postoperative serum bilirubin level three months after the portoenterostomy is predictive for improved survival without liver transplantation in the first two years of life.[15,32] In our study population, the mean conjugated serum bilirubin level three months after Kasai operation was rather high. Only 3 of 11 patients (27 %) are still living with native liver after the portoenterostomy.

Among the determinants of portoenterostomy outcome, the one we can influence is the age at referral and thus the age at procedure. Therefore, much interest in the countries with high incidence of the disease is focused on establishing early diagnosis. In Taiwan they started using infant stool colour cards for universal screening for BA, which help the parents in identifying acholic stools. By this, the referral and operation was earlier and the outcome of the procedure better.[13] The next promising screening strategy is early measurement of serum conjugated bilirubin.[33] Also in Slovenia the suspicion for the disease might be increased with the use of the screening tools.

In conclusion, the incidence of BA in Slovenia is among the lowest in the world population. In addition, BASM form is very rare in the Slovenian cohort of children with BA. The newborns were born mature and healthy despite the fact that most of them became jaundiced in the first days of life, which can be a predictor of early liver damage. The seasonal incidence of BA might suggest the viral aetiology of the disease. The outcome of children with biliary atresia is related to the time of referral, age when they have their primary surgery, postsurgical management and timely referral to liver transplantation.

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