Correlation of intrahepatic biliary cysts and the time of liver failure in biliary atresia after Kasai procedure

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To the Editor: Biliary atresia (BA) is a biliary obstruction disease that affects the lives of infants and young children. Kasai procedure (KP) improves the outcomes of BA, but it has not successfully solved various problems of BA with postoperative inflammation of bile duct and liver fibrosis, intrahepatic bile duct cystic expansion (intrahepatic biliary cysts, IBC), portal hypertension, liver function failure, *etc*. As a result, most of the children still need liver transplantation (LT).[1] In recent years, cystic dilatation of the intrahepatic bile duct, which may be an important factor of prognosis, has been paid more attention by surgeons with the development of imaging technique. This study aimed to analyze the relationship among the formation characteristics and pathological manifestations of IBC, the bilirubin level, and the time to the end-stage liver function after KP.

The main hospital that carried out this study was Tianjin Children's Hospital. The study complied with the *Declaration of Helsinki* and was approved by its Review Board of Ethics Committee (No. TCH-20170152). The Ethics Committees of Wuhan Children's Hospital, Tianjin First Central Hospital, and Children's Hospital of Anhui Province have also been informed of research content and approved to cooperate in this study. The patients or their parents or legal guardians provided verbal consent for their non-identifiable data to be collected and analyzed within this study on their behalf.

The clinical data were collected during January 2008 and December 2018 from Tianjin First Central Hospital, Tianjin Children's Hospital, Wuhan Children's Hospital, and Children's Hospital of Anhui Province, respectively. A total of 179 cases that had LT for the hepatic failure of BA were enrolled, all patients were diagnosed with type III of BA within 3 months after the birth and experienced KP. The criteria for enrollment were complications of end-stage cirrhosis. The latest laboratory test before LT was chosen for the comparison. Computed tomography (CT) examination within 1 month before LT was conducted to determine the existence of intrahepatic bile duct cystic expansion. The presence of IBC was defined as positive if an IBC (1 cm in diameter) was detected by CT examination. Fifty of 179 patients' samples were randomly selected for hematoxylin and eosin (H&E) staining to compare the pathological characteristic of IBC (+) with IBC (−) group. The occurrence of liver fibrosis, bile duct hyperplasia, cholangitis, and ductal plate malformation (DPM) were investigated.

Liver tissue samples were collected from the whole native livers during transplantation. Biopsies of the right lobe of BA livers were processed for H&E staining according to the standard protocol. Liver fibrosis degree was classified into seven grades according to the METAVIR fibrosis grading standard.[2] According to the Laennec subclassification method, it could be further divided into three substages of mild, moderate, and severe cirrhosis, respectively. Five vision field of portal tracts were randomly selected under the high-time microscopy to quantify the number and average of bile ducts, bile duct hyperplasia degree was then classified into grade 0: < 5 bile duct structures per average vision field; grade 1: 5–9 proliferative bile ducts per average vision field; grade 2: $\geq$10 proliferative bile ducts per average vision field; and grade 3: $\geq$10 proliferative bile ducts, with abnormal distortion and small morphology of the hyperplasia bile ducts per average vision field.[3] Bileplug was classified into

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level 1: no bileplug in portal tracts; level 2: only a few bileplug in portal tracts; level 3: a small number of bileplug in each portal tract; and level 4: almost all small bile ducts in the portal tracts had bileplug. Bile duct plate malformation was defined according to the presence of DPM,[4] the score was $Z = 2$ as presence and $Z = 1$ as absence.

Statistical analyses displayed in tables were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). The continuous variables of normal distribution were represented as mean (standard deviation) and further compared using independent *t*-tests. The continuous variables of skewness distribution were tested by Mann-Whitney *U* tests. Categorical variables were represented as percentages. A Chi-square test was used to determine the distribution of categorical variables among various groups. A two-sided *P* value (<0.05) was considered to be of statistical significance.

A total of 179 patients with 75 males and 104 females who accepted LT after KP were enrolled in this study, 50 liver tissues were collected for pathological examination at the same time. As shown in Table 1, 36 patients were detected intrahepatic cyst with bile duct expansion, namely the IBC (+) group, the remaining 143 cases were classified into the IBC (−) group. Fifty pathological examinations show that 18 cases were in the IBC (+) group and 32 cases were in the IBC (−) group. There were 27 (27/36, 75.0%) female patients in the IBC (+) group and 77 (77/143, 53.5%) female patients in the IBC (−) group ($P = 0.021$). The average KP age in the IBC (+) group (71.36 days) was slightly higher than that in the IBC (−) group (62.76 days), but the incidence of postoperative cholangitis in the IBC (+) group (75.0%) showed no difference compared to that in the IBC (−) group (76.2%).

Supplementary Figure 1, http://links.lww.com/CM9/A402 showed that most of the intrahepatic bile ducts in the IBC (+) group were fusiform dilated which was distributed along with the Gleason sheath in the middle lobe of the liver, and even some of the dilated bile ducts had bead-like changes.

Comparison of liver function before LT showed that the test indexes of the IBC (+) group were lower than that of the IBC (−) group except total bile acid (TBA) and lactate dehydrogenase (LDH), and the levels of total bilirubin (TB) and direct bilirubin (DB) were significantly higher in the IBC (−) group ($P < 0.05$). There was no significant difference in renal function and blood tests between the two groups [Table 1].

Fifty cases of H&E staining showed that there were irregular bile lakes with bile-like crystals surrounded by fibrous tissue, and severe fibrosis in the IBC (+) group, no typical bile duct epithelioid structure was observed [Supplementary Figure 2, http://links.lww.com/CM9/A402]. The degree of liver fibrosis, bile duct hyperplasia, and incidence of DPM had no statistical significance between the two groups. However, the bile plug was relatively mild in the IBC (+) group ($P = 0.013$) [Supplementary Table 1, http://links.lww.com/CM9/A402 and Supplementary Figure 3, http://links.lww.com/CM9/A402].

The median time of liver failure (TLF) of the IBC (+) group was 11.50 months, which was significantly higher than the IBC (−) group of 9.00 months. The curve indicated that the IBC (+) group had better TLF than the IBC (−) group ($P = 0.038$) [Supplementary Figure 4, http://links.lww.com/CM9/A402].

Image examinations such as B-ultrasound, CT, and magnetic resonance imaging (MRI) are the main methods for diagnosing IBC after KP. At present, the incidence of IBC is widely reported by various medical centers. Since the initial case report, the morbidity has gradually increased from 6% to 58%, which might be due to the technical progress of imaging. Some asymptomatic IBC was diagnosed accidentally in prospective studies, the overall incidence is about 23%,[5] which was consistent with the incidence (20.1%) in our study. We also observed that only a small number of dilated bile ducts were located in the peripheral zone, while most of the IBC were located in the middle lobe of the liver with a fusiform distribution along the portal vein.

There have been many hypotheses about the possible causes and mechanisms of IBC. The widely accepted theory is that IBC occurred with an increased local inflammatory response, bile duct edema, stricture, poor bile drainage, and then the formation of intrahepatic bile duct dilatation.

Table 1: Characteristics of 179 participants that had liver transplantation for the hepatic failure of biliary atresia.

Characteristics	IBC positive ($n = 36$)	IBC negative ($n = 143$)	*P* values
AKP	71.36 ± 28.68	62.76 ± 18.35	0.094
Female	27 (75.0)	77 (53.8)	0.021
Cholangitis	27 (75.0)	109 (76.2)	0.878
Laboratory tests			
Alanine transaminase (U/L)	68.95 (45.75, 123.95)	108.90 (68.55, 189.00)	0.006
Aspartate transaminase (U/L)	137.15 (94.63, 199.00)	207.60 (120.35, 340.65)	0.032
Total bilirubin (μmol/L)	72.58 (25.57, 263.39)	210.41 (72.34, 321.59)	0.021
Indirect bilirubin (μmol/L)	23.12 (8.21, 55.21)	32.41 (11.08, 64.50)	0.634
Direct bilirubin (μmol/L)	59.22 (16.46, 175.32)	166.29 (50.10, 250.07)	0.008

Data are presented as mean ± standard deviation, *n* (%) or median (interquatile). IBC: Intrahepatic biliary cyst; AKP: Age at Kasai portoenterostomy in days.

The development of BA is a sustained progress of liver fibrosis, biliary epithelial cells damage, and bile leakage, then forms a bile duct expansion, with pathological changes throughout the embryonic, neonatal and even infant stages. Whether there is a correlation between operation and postoperative bile drainage unobstructed remains unclear. In addition, it has been found that biliary dysplasia, the presence of DPM, is associated with the formation of IBC. Based on the above assumptions, we found the incidence of cholangitis and DPM in both groups was high, and the difference between the groups was not statistically significant, suggesting that the formation of IBC may be related to factors other than cholangitis or DPM.

In the study, we found that the levels of alanine transaminase, aspartate transaminase, TB and DB in the IBC (+) group were lower than those in the IBC (−) group, besides, the IBC (+) group showed a lower degree of cholestasis, with statistically significant difference. Possible explanations for this phenomenon are: (i) Bile duct epithelial cells can be observed on the inner wall of the cyst, and a large number of proliferating immature bile duct epithelial cells can be seen in the surrounding hepatic lobules. The dilated IBC and new bile ducts might provide a room for bile to alleviate cholestasis. (ii) The cyst was found to be in communication with the jejunal bile branch by angiography.[6] These phenomena might be indicated that the dilated bile duct located in the middle of the liver along the portal vein can promote bile discharge, reduce cholestasis, and play a positive role in the compensation of liver function.

The pathophysiology of IBC is also related to the outcome. Previous studies have shown that the presence of IBC is an important factor affecting the survival of the native liver. However, others found that the poor prognosis in IBC (+) and IBC (−) groups was 47% and 53%, respectively,[6] that is, whether bile duct dilation occurs or not affects the TLF of children, and the long-term prognosis of BA after KP does not necessarily depend on the development of IBC. The current opinion takes presence of IBC as a risk factor for cholangitis and long-term survival.[7,8] However, in short term, we found that the postoperative TLF in the IBC (+) group is longer than the IBC (−) group, the occurrence of IBC (+) can play a positive role for bile drainage, reduce bilirubin damage to the liver, and prolong the TLF. However, it is still not clear whether the cystic expansion of intrahepatic bile duct affects the long-term prognosis of IBC (+) patients after KP.

In conclusion, compared to the common view, it seems that during the period of post-KP to the native liver failure, the formation of IBC may be the reason for lowering blood bilirubin levels, reducing the grade of liver bile plug, and prolonging the TLF. The formation of IBC may be related to factors other than cholangitis and DPM, but the clear pathogenesis and pathophysiological changes still need to be explored.

Conflicts of interest

None.

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