Pediatric Surgery International (2018) 34:381–386
https://doi.org/10.1007/s00383-018-4231-7

ORIGINAL ARTICLE

Clinical and pathological features of patients with biliary atresia who survived for more than 5 years with native liver

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Accepted: 20 January 2018 / Published online: 9 February 2018

Abstract

Purpose The objective of this study was to determine the predictive index for prognosis in patients with biliary atresia (BA).

Methods A total of 71 patients were divided into two groups. Group A included 39 postoperative BA patients who survived for more than 5 years with normal liver function and did not present cirrhosis, and group B included 32 patients who died from liver failure within 1 year after surgery. The clinical data of the two study groups were compared, and liver pathology was evaluated using a scoring system.

Results The average age and weight were similar in the two groups (64.1 ± 16.8 days vs. 60.7 ± 19.3 days, $p > 0.05$; 4.9 ± 0.9 kg vs. 4.7 ± 0.8 kg, $p > 0.05$). There were no significant intergroup differences in preoperative total bilirubin (TB), direct bilirubin (DB), alanine transaminase, aspartate transaminase, and international normalized ratio. The preoperative levels of gamma-glutamyl transpeptidase (γ-GT) and albumin in group A were significantly higher than those in group B (γ-GT: 956.8 ± 503.8 IU/L vs. 620.2 ± 437.1 IU/L, $p = 0.00$; ALB: 40.8 ± 2.5 g/L vs. 36.8 ± 3.6 g/L, $p = 0.04$), whereas alkaline phosphatase was significantly lower in group A compared to group B (512.2 ± 224.6 IU/L vs. 631.7 ± 254.7 IU/L, $p = 0.02$). The postoperative TB and DB after 2 weeks of the Kasai procedure decreased significantly more in group A than in group B (TB: 53.9 vs. 21.4%, $p = 0.00$; DB: 51.0 vs. 22.7%, $p = 0.00$), whereas γ-GT increased significantly less in group A than in group B (48.3 vs. 142.1%, $p = 0.00$). Cystic structures were observed at the porta hepatis on ultrasound in more patients from group A (28.2 vs. 3.2%, $p < 0.00$). There was no significant difference in the total pathological score between the two groups ($p = 0.38$) whereas the score of bile plugs was significantly higher in group A (0.95 vs. 0.38, $p = 0.03$).

Conclusion The cystic structures observed at the porta hepatis on ultrasound preoperatively and the rapid decrease in TB and DB within 2 weeks postoperatively predict good long-term prognosis, whereas a significant increase in γ-GT with a lower preoperative level predicts poor long-term prognosis. The development of bile plugs may be an indicator of favorable prognosis.

Keywords Biliary atresia · Prognosis · Pathology · Liver function · Ultrasound

Introduction

Biliary atresia (BA) is the most common biliary obstructive disease [1] and the most common cause of pathological jaundice in infants [2]. The morbidity of BA is approximately 1/12,000 in the United States and the United Kingdom, 1/9600 in Japan, and 1/5000–1/8000 in China, demonstrating that the condition is higher in Asia than in Europe and North America [1, 3]. As the main pathological characteristics of BA, atresia of intra- and extra-hepatic bile ducts and progressive liver fibrosis lead to fatal liver cirrhosis and liver failure before the age of 2 years [4–6] if left untreated. The prompt execution of the Kasai procedure (≤ 90 days) is the standard treatment. However, only 30% of the patients who undergo this procedure achieve long-term survival with native liver [1], whereas the remaining patients need liver transplantation. Few patients undergo liver transplantation in mainland China because of the shortage of organ donors. For most BA patients, a successful and effective Kasai procedure is the only chance of survival; however, the prognosis of

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BA after this procedure varies considerably. Therefore, the accurate prediction of the long-term outcome during the assessment before or immediately after the Kasai procedure is essential for establishing future therapeutic strategies. The patients who are predicted with no effect to Kasai procedure can avoid unnecessary surgical trauma and high treatment costs, whereas patients with poor long-term prognosis and who need liver transplantation can be included in the waiting list for liver transplantation as early as possible. The perioperative clinical data and liver pathology of patients with different outcomes were retrospectively compared in this study to determine the predictive index from perioperative examinations.

Materials and methods

Clinical data

The clinical data of patients who were diagnosed with type III BA by surgical exploration and who underwent the Kasai procedure from January 2006 to November 2010 in Children's Hospital of Fudan University were collected. The patients with excellent or poor outcome were recruited and divided into two groups: patients who survived for more than 5 years and presented normal values in the main liver function test, including total bilirubin (TB), direct bilirubin (DB), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (γ-GT), and albumin (ALB), and no evidence of liver cirrhosis by physical examination or ultrasound, were recruited into a good prognosis group (group A). The patients who were treated in the same period and died from liver failure within 1 year after Kasai surgery were included in the poor prognosis group (group B). Postoperatively, all these patients were treated according to the protocol available at that time. Briefly, methylprednisolone was intravenously infused at a dose of 4 mg/kg/day for 3 days, and then decreased to 3 mg/kg/day for another 3 days. After that, long-term oral administration of methylprednisolone was given at a dose of 2 mg/kg/day and was decreased over time on the basis of jaundice clearance. Intravenous antibiotics (ceftriaxone or imipenem) were administered after surgery for 1 month before oral cotrimoxazole and cefaclor until 6 months after surgery. Ursodesoxycholic acid was routinely dosed for 3–6 months on the basis of jaundice clearance. The exclusion criteria were survival for more than 5 years with progressive liver cirrhosis or continuous or intermittent abnormal liver function, death from intestinal obstruction, severe infections, other complications, absence of routine follow-up, and absence of treatment according to our guideline.

Table 1 Preoperative clinical parameters

Parameters	Group A ($n=39$)	Group B ($n=32$)
Age at surgery (days)	64.1 ± 16.8	60.7 ± 19.3
Weight at surgery (kg)	4.9 ± 0.9	4.7 ± 0.8
Age at onset of jaundice (days)	4	3.5
TB (μmol/L)	183.1 ± 75.6	174.4 ± 79.7
DB (μmol/L)	136.8 ± 55.8	142.7 ± 52.6
ALT (IU/L)	106.8 ± 62.4	120.6 ± 82.0
AST (IU/L)	148.4 ± 72.5	174.7 ± 123.3
γ-GT (IU/L)*	956.8 ± 503.8	620.2 ± 437.1
ALP (IU/L)*	512.2 ± 224.6	631.7 ± 254.7
ALB (g/L)*	40.8 ± 2.5	36.8 ± 3.6

*p value < 0.05

Methods

Basic data including gender, weight, age at onset of jaundice, and age and weight at the time of surgery were collected and compared. The main liver function tests and coagulation function indexes, including TB, DB, ALT, AST, alkaline phosphatase (ALP), γ-GT, ALB, and international normalized ratio (INR), were compared between the two groups. Using end-expiratory imaging, the liver size below the right costal margin at the mid-clavicular line and the structure of the hepatic portal system were observed on ultrasound and measured before the Kasai operation, and ultrasound data were collected in the two groups and analyzed. As we have previously reported [7], eight pathological features—liver fibrosis, bile duct proliferation, bile plugs in portal ductules, cholestasis, hepatocyte degeneration, inflammatory cell infiltration in portal areas, extra-medullary hematopoiesis, and ductal plate malformation (DPM)—were included in a 21-point (0–21) scoring system. The pathological liver sections were evaluated by two attending or chief pathologists who were double blinded to the scoring system. The mean scores of the two pathologists were compared. A t test was applied to compare differences in the measurement data. A Chi-square test was applied to analyze the enumeration data. This study was approved by the Research Ethics Committee of Children's Hospital of Fudan University.

Results

A total of 18 boys and 21 girls were included in group A whereas 18 boys and 14 girls were included in group B. The average age and weight at surgery was 64.1 ± 16.8 days and 4.9 ± 0.9 kg in group A versus

Table 2 Changes in clinical parameters 2 weeks after the Kasai procedure

Parameters	Group A (%)	Group B (%)
TB*	–53.9	–21.4
DB*	–51.0	–22.7
ALT	10.3	15.5
AST	–13.8	–8.7
GGT*	48.3	142.1
ALP	–18.2	–24.7
ALB	–3.9	–1.8

*p value < 0.05

Table 3 Presence of cystic structures at the porta hepatis on preoperative ultrasound

Variables	Presence of cystic structure	Absence of cystic structure	Percentage (%)*
Group A	11	28	28.2
Group B	1	31	3.2
Total	12	59	

*p value < 0.05

60.7 ± 19.3 days and 4.7 ± 0.8 kg in group B. The median age at onset of jaundice was 4.0 days in group A and 3.5 days in group B. There was no significant difference ($p < 0.05$) in the clinical parameters between the two groups (Table 1).

There was no significant intergroup differences in preoperative TB (183.1 ± 75.6 vs. 174.4 ± 79.7 μmol/L), DB (136.8 ± 55.8 vs. 142.7 ± 52.6 μmol/L), ALT (106.8 ± 62.4 vs. 120.6 ± 82.0 IU/L), AST (148.4 ± 72.5 vs. 174.7 ± 123.3 IU/L), and INR (0.97 ± 0.09 vs. 0.94 ± 0.12). The preoperative levels of γ-GT and albumin in group A were significantly higher in group A than in group B (γ-GT: 956.8 ± 503.8 vs. 620.2 ± 437.1 IU/L, $p = 0.00$; ALB: 40.8 ± 2.5 vs. 36.8 ± 3.6 g/L, $p = 0.04$), whereas ALP was comparatively lower in group A (512.2 ± 224.6 vs. 631.7 ± 254.7 IU/L, $p = 0.02$) (Table 1).

The postoperative levels of TB and DB after 2 weeks of the Kasai procedure decreased significantly more in group A than in group B (TB: 53.9 vs. 21.4%, $p = 0.00$; DB: 51.0 vs. 22.7%, $p = 0.00$) whereas γ-GT increased less in group A than in group B (48.3 vs. 142.1%, $p = 0.00$) (Table 2).

Using end-expiratory imaging, the liver size below the right costal margin at the mid-clavicular line on preoperative ultrasound was similar between group A and B (34.8 ± 8.0 vs. 36.5 ± 10.7 mm). The rate of diagnosis of cystic structures at the porta hepatis on preoperative ultrasound was significantly different between the groups ($p < 0.01$), corresponding to 28.2% (11 of 39) in group A and 3.2% (1 of 32) in group B (Table 3).

Table 4 Pathological score of liver sections

Pathological features	Group A ($n = 39$)	Group B ($n = 32$)
Liver fibrosis	2.28	2.66
Bile duct proliferation	1.74	1.69
Bile plugs in portal ductules*	0.95	0.38
Cholestasis	2.95	3.00
Hepatocyte degeneration	2.10	2.31
Inflammatory cell infiltration in portal areas	1.87	1.56
Extramedullary hematopoiesis	0.36	0.41
Ductal plate malformation	0.23	0.31
Total	12.48	12.32

*p value < 0.05

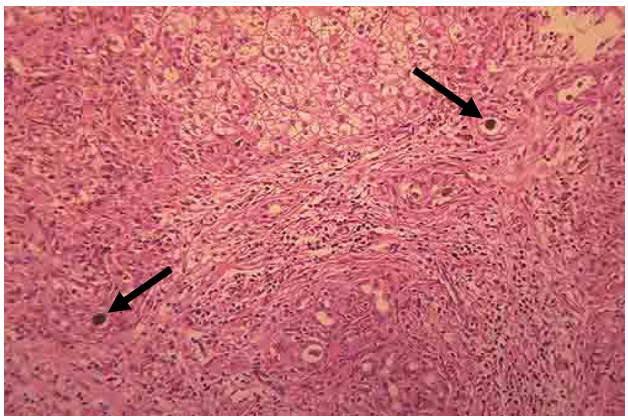

Fig. 1 The brown spots indicated by the black arrows are bile plugs in portal ductules, which appeared more frequently in group A than in group B

There was no significant difference in the total pathological score between the two groups (12.48 vs. 12.32, $p = 0.38$). The average scores of liver fibrosis, bile duct proliferation, cholestasis, hepatocyte degeneration, inflammatory cell infiltration in portal areas, extra-medullary hematopoiesis, and DPM were similar between the two groups ($p > 0.05$). However, the score of bile plugs in portal ductules was significantly higher in group A (0.95 vs. 0.38, $p = 0.00$) (Table 4; Fig. 1).

Discussion

The therapeutic effect of the Kasai procedure for BA varies considerably, and no predictive index for prognosis has been determined to date. Some clinical studies have investigated the correlation between prognosis and age at surgery [8,

9], the postoperative level of bilirubin and transaminase at short-term follow-up [10–12], the onset of reflux cholangitis postoperatively [13], and liver pathology [12, 14]. However, there is still no consensus on prognostic indicators of BA.

Of the potential predictive indicators, age at surgery attracts much attention of pediatric surgeons. Based on the results of several large sample studies [15–17], many authors have accepted that older age at the time of surgery is associated with a poorer outcome in infants who undergo the Kasai procedure. Some medical centers recommend that liver transplantation be performed directly in patients older than 90 days rather than performing the Kasai procedure first. However, other studies involving infants who underwent the Kasai procedure at an age older than 90 or 100 days were contradictory [18, 19] and concluded that the outcome of these patients was not significantly different from that of younger patients. Similarly, our results revealed that there was no significant difference in the age at surgery between the two groups, and one patient who underwent the Kasai procedure at age > 100 days had good prognosis. Moreover, the percentage of patients older than 60 days at surgery was similar between the two groups. Therefore, older age is not a sufficient reason for not performing the Kasai procedure.

Liver function is another important potential prognostic and predictive indicator. The shorter term decrease in bilirubin after operation has been one of the most studied indexes. Choosily conducted a prognostic study involving 133 patients with BA and observed that the patients whose TB was decreased by 20% at 7 days after the Kasai procedure had a significantly higher 5-year survival rate than other patients [20]. Another study [21] reported that infants whose TB did not fall below 2.0 mg/dL within 3 months of the Kasai procedure had a higher risk of early disease progression and suggested that these patients should be considered for LT promptly. Goda performed a ROC analysis and concluded that the combination of serum DB and AST (with levels lower than 0.7 mg/dL and 94 IU/L, respectively) at 2 months after the Kasai operation was a reliable predictor of long-term outcome for BA [10]. Rodeck observed that a serum bilirubin concentration lower than 57 μmol/L at 6 weeks after the Kasai operation was an early predictor of surgical success and that children whose bilirubin concentrations were higher than this level should be carefully and constantly monitored for the need for transplantation to optimize pretransplant management [22]. The results of this study indicated that TB and DB levels were decreased by more than 50% in patients with good outcomes. Therefore, the rapid decrease of these markers immediately after the Kasai procedure is a reliable predictor of good long-term prognosis. γ-GT has been frequently used as a diagnostic index to differentiate BA from other cholestatic diseases but has been rarely used as a prognostic index. It has been reported [23] that the increase in AST and γ-GT levels appears to be an early indicator of risk of liver transplantation during the follow-up of jaundice-free patients after successful Kasai procedures. Our results indicated that γ-GT was increased rapidly after the operation, and the preoperative level was low in patients with poor outcome, which confirms that the short-term increase in γ-GT after the Kasai procedure may be an indicator of poor prognosis.

The correlation between liver pathology—the most controversial index—and prognosis has been repeatedly reported in the literature. DPM, severe liver fibrosis, bile duct proliferation, and cholestasis were the best studied pathologic features, and most studies confirmed that the presence of these features predicted poor prognosis [14, 19, 24]. However, Santos reported that the prognosis of BA was associated with bile duct proliferation but not with the degree of liver fibrosis [25]. Other studies have reached contradicting conclusions. A study involving 142 patients investigated the correlation between prognosis and 16 pathological features, including liver fibrosis, interlobular inflammation, DPM, bile duct proliferation, and bile plugs in portal ductules, among others, and found no statistical correlation between these features. The authors concluded that the value of liver pathology during the Kasai procedure in predicting the outcome of BA patients was limited [26]. Similarly, Arii and Vuković found no correlation between DPM and prognosis [27, 28]. Our results indicated that there was no significant difference between patients with excellent outcome and those with poor outcome, except for the presence of bile plugs in portal ductules. In this respect, we hypothesize that bile plugs may be associated with well-developed cholangioles, which may be the cause of higher scores in patients with good outcome. However, this hypothesis needs to be confirmed by large sample studies. Other studies reported that better defined pathological features were associated with prognosis. Longo-Santos [29] found that the early deposition of type I collagen around the hepatic sinus was associated with poor prognosis in BA. Mirza [30] and Sanghai [31] measured the size of small bile ducts and concluded that the patients with larger diameter bile ducts had better prognosis than those with smaller diameter bile ducts. However, there is still no consensus on these non-classical pathological features.

Ultrasound examination is performed routinely as an auxiliary diagnostic method and is essential for the differentiation between BA and other cholestatic liver diseases. Triangular cord sign [32, 33], small-sized and irregular gallbladder, hepatic artery enlargement [34], and hepatic subcapsular flow [35] are signs of BA. However, ultrasound has not been reported to be a predictor of prognosis to date. Our results indicated that several patients in the good prognostic group presented cystic structures at the porta hepatis. However, most of the examined cystic structures were pseudocysts, which were edematous and contained loose fibrous

tissue but did not have a lumen, and a large amount of yellow bile-like fluid was discharged with high hydrostatic pressure upon the excision of cystic structures. In addition, our data showed that the postoperative TB and DB declined over 60% within 2 weeks in all the patients with cystic structure. Therefore, these patients tend to have a high-fluid bile and eliminate jaundice immediately after the Kasai procedure. These characteristics may be the underlying cause of good outcomes in patients with pseudocysts. Therefore, cystic structures at the porta hepatis detected on preoperative ultrasound may be a predictor of good long-term prognosis.

To improve the sensitivity of the analysis, only the patients with excellent and very poor outcome were included in this study. However, the outcome of several patients ranged between these two extremes, including patient survival for more than 5 years with progressive liver cirrhosis or continuous or intermittent abnormal liver function, death from liver failure more than 1 year after surgery. This limitation may reduce the applicability of our conclusions. Moreover, our results need to be confirmed by studies with larger sample size and longer follow-up.

In conclusion, the observation of cystic structures at the porta hepatis on preoperative ultrasound and the rapid decrease in TB and DB within 2 weeks after the Kasai procedure may predict good long-term prognosis. A significant increase in γ-GT with lower preoperative level may predict poor long-term prognosis. The development of bile plugs may be an indicator of favorable prognosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human and animal participants This article does not contain any studies with human participants or animals performed by any of the authors.

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