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ORIGINAL ARTICLE

Long-term results of biliary atresia in the era of liver transplantation

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Abstract
Purpose The purpose of this study was to analyze the survival of patients with biliary atresia (BA) after Kasai operation and liver transplantation (LT) and to analyze the factors affecting survival.
Methods Seventy-two patients diagnosed with BA were operated on between April 1995 and December 2009 and retrospectively analyzed.
Results Out of the 72 patients, 59 received Kasai operation and 13 received LT without prior Kasai operation. Twenty-seven patients received LT after Kasai operation. Survival with native liver was 39 % at 10 years. With the application of LT, overall 10-year survival for patients with BA was 94.9 %. Among patients alive with native livers after Kasai operation, 14 patients (58.3 %) have at least one complication associated with biliary cirrhosis and portal hypertension. Age at which Kasai operation was performed (60 days) and postoperative normalization of bilirubin were independent risk factors for survival with the native liver, according to multivariate analysis (HR 2.90, $p = 0.033$ and HR 9.89, $p = 0.002$).
Conclusions Survival of BA patients has greatly increased in the era of LT. However, many patients surviving with native livers after Kasai operation continue to have signs of biliary cirrhosis and abnormal liver function.

Keywords Biliary atresia · Pediatric · Liver transplantation · Kasai operation

Introduction

Biliary atresia (BA) is a rare condition in which progressive fibrosis of the biliary tree in the newborn leads to bile duct obstruction and subsequent liver cirrhosis. The etiology underlying this progressive biliary fibrosis is still unknown and if left untreated, inevitably leads to patient death. The Kasai operation, introduced in 1959 by Kasai and Suzuki, has since been widely accepted as the primary method of surgical treatment for BA. However, approximately 66 % of patients still suffer from insufficient biliary excretion, and long-term survival after Kasai operation is reported to be below 50 % [1–7]. In recent years, liver transplantation (LT) has been applied to BA patients with rapidly progressing cirrhosis requiring primary treatment or with sustained biliary obstruction following Kasai operation. This treatment strategy has raised the long-term survival of BA patients to above 90 % [8–10]. The present study describes the real-world experience of surgical treatment of BA patients in a single center in the era of LT and examines the factors affecting patient survival.

Patients and methods

Patients who were diagnosed with BA and underwent surgical intervention (Kasai operation or LT) between

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April 1995 and December 2009 at a tertiary referral center in Seoul, South Korea (Samsung Medical Center) were included in this analysis. Patients were excluded from the analysis, if they were referred to our center after having received treatment for BA at an outside hospital. Kasai operation was the surgical strategy initially considered in all cases. However, for patients who had already developed complications related to liver cirrhosis and portal hypertension at the time of diagnosis of BA, LT was elected without initial Kasai operation. After Kasai operation, patients were closely followed and in case of recurrent episodes of cholangitis, progressive jaundice, signs of portal hypertension (ascites, variceal bleeding), and growth or developmental failure, the patient was referred for LT. All surgeries were performed by a single surgeon (S. K. L), experienced in both pediatric surgery and transplant surgery. In earlier cases of Kasai operation, technique for portoenterostomy was interrupted sutures with 4–0 silk. Recently, we have switched to continuous suturing with 6–0 polydioxanone (PDS). Otherwise, there have been no significant changes in surgical technique for Kasai operation or LT during the study period. In LT, the donor's left lateral section of the liver was used in most cases and the graft was anastomosed to the recipient's inferior vena cava using piggy-back technique.

Postoperative care of patients was done according to standardized in-house protocol, which remained unchanged during the study period. As post-Kasai management, patients were given sulfamethoxazole/trimethoprim, phenobarbital for 6 months, and prednisolone starting at postoperative day 7, then tapered within 1 week. Ursodeoxycholic acid and multivitamins were also given. For post-LT maintenance immunosuppression 2-drug or 3-drug regimen of a calcineurin inhibitor, steroids with or without mycophenolate mofetil are used. No induction therapy was done.

Patient data including gender, body weight and gestational age at birth, age at operation, outcome, and complication following operation were retrospectively analyzed by reviewing the medical records. Preoperative evaluation included clinical exam and laboratory tests, ultrasonography, magnetic resonance imaging (MRI), and liver biopsy. The final diagnosis of BA was made at the time of the operation according to operative findings including operative cholangiogram and pathologic examination.

Growth retardation at time of LT was defined as below −2 standard deviations (SD) of body weight or height adjusted for age. Treatment failure of Kasai operation was defined as patient death or the patient needing and receiving an LT. Survival time was calculated from birth to the occurrence of a specified event. Survival was analyzed by Kaplan–Meier analysis and factors affecting survival were examined using log-rank test and Cox proportional hazard model.

Results

From April 1995 to December 2009, 72 patients were diagnosed with BA at Samsung Medical Center. The patients included 24 boys (33.3 %) and 48 girls (66.7 %). The median birth weight was 3100 ± 526 g and there were five premature children born before the 37th gestational week. Fifty-nine of the 72 patients received Kasai operation as the primary treatment and the median patient age at Kasai operation was 70 days (range 17–166 days). In 13 patients, LT was performed as the primary treatment of BA. The median follow-up time for the patients was 77 months (range 2 months–15 years 7 months). The median time interval from Kasai operation to LT was 6.2 months (range 1.6–99.5 months, Table 1).

Figure 1 outlines the patient population of this study. Out of the 32 patients who received Kasai operation and did not go on to receive LT, 24 patients are being followed regularly in the outpatient clinic: however, 14 patients (58.3 %) have at least one complication associated with biliary cirrhosis and portal hypertension. A similar trend is observed between patients younger than 10 years or older than 10 years of age (Table 2). Three patients died at 2, 24, and 49 months after Kasai operation due to liver failure, respectively. Five patients were lost to follow-up: three patients out of the five who were lost to follow-up had normal liver function when they last visited the clinic at 38, 70 and 64 months after Kasai operation. The other two patients were listed for LT at 9 and 11 months following Kasai operation but did not go on to receive LT.

A total of 40 patients received LT (37 living donor LT, 3 deceased donor LT). Thirty-nine out of 40 patients who received LT for BA are alive at median 7.8 years following LT. One patient died at 3 months post-transplant due to graft failure from CMV disease. Among the 39 survivors of LT, two patients received 2nd LTs for graft failure due to hepatic artery thrombosis and biliary cirrhosis, respectively. Complications observed in LT recipients of BA are listed in Table 3. Aside from one case in which *de novo* autoimmune hepatitis is gradually compromising graft function, 38 out of the 39 survivors of LT currently have normal functioning liver grafts (including two re-transplant cases).

The survival curves of 72 patients who were treated for BA are shown in Fig. 2a. With Kasai operation as the only means of surgical treatment, survival of patients with their native livers (time from birth to LT or death) is 39 % at 10 years. However, the overall survival of patients is approximately 95 % at 10 years, when both Kasai operation and LT are utilized as treatment modalities (Fig. 2b).

Post-Kasai operation survival, defined as the time from Kasai operation to LT, was superior in the 21 patients who received Kasai operation before 60 days of age than those

Table 1 Characteristics of patient with biliary atresia

	$N = 72$
Males:females	24:48
Median birth weight (g) ± SD	3100 ± 526
Median gestational age ± SD	39 ± 1.64
Median age at Kasai operation (days)	70 (17 ~ 166)
Age at Kasai operation	
≤60 days	21 (35.6 %)
61 ~ 90	27 (45.8 %)
>90 days	11 (18.6 %)
Median age at LT (months)	8.8 (3.9 ~ 101.0)
Median interval from Kasai operation to LT (months)	6.2 (1.6–99.5)
Median follow-up period (months)	77 (2 ~ 189)
Median age at last follow-up (months)	81 (7 ~ 191)

LT liver transplantation

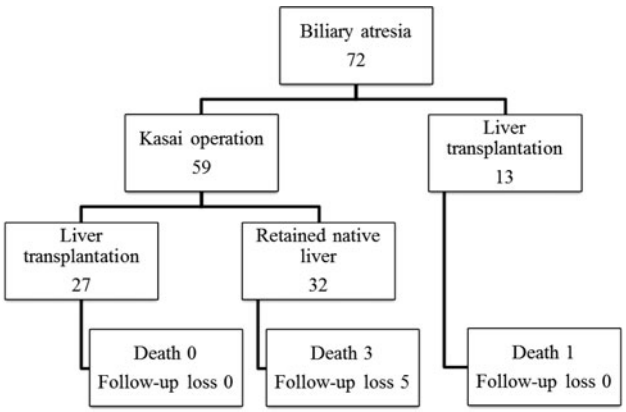

Fig. 1 Long-term results of biliary atresia

Table 2 Clinical features of patients alive with functioning native livers after Kasai operation

	Overall ($N = 24$)	Age <10 years ($N = 11$)	Age ≥10 years ($N = 13$)
Complications of cirrhosis			
Yes	14 (58.3)	8 (61.5)	8 (54.5)
No	10 (41.7)	5 (38.5)	3 (45.5)
Esophageal varices[a]			
Yes	7 (29.2)	4 (30.8)	4 (27.3)
No	17 (70.8)	9 (69.2)	7 (72.7)
Splenomegaly[b] and thrombocytopenia			
Yes	12 (50.0)	7 (53.8)	7 (45.5)
No	12 (50.0)	6 (46.2)	4 (54.5)
Ascites			
Yes	2 (8.3)	2 (15.4)	0
No	22 (91.7)	11 (64.6)	11 (100.0)

[a] Detected by endoscopy

[b] Measured by ultrasonography

Table 3 Complications in recipients of liver transplantation for biliary atresia

	N
Vascular complications	
Portal vein stenosis	4
Portal vein thrombosis	2
Hepatic artery thrombosis	1
Biliary stricture	2
De novo autoimmune hepatitis	3
Post-transplant lymphoproliferative disease	3
Diaphragmatic hernia	1
Gastric varix bleeding	1
Re-transplant	2

who received Kasai operation later than 60 days after birth ($p = 0.004$). Patients whose serum bilirubin levels were below 1.5 mg/dl at 2 months post-Kasai operation showed better survival than those who did not experience normalization of bilirubin levels ($p = 0.002$). Postoperative ascending cholangitis was observed in 30 out of the 59 patients (50.8 %) following Kasai operation. Sixteen patients had single episodes and 14 patients had multiple episodes of ascending cholangitis. However, the presence or frequency of ascending cholangitis was not related to the survival of the native liver following Kasai operation ($p = 0.319$, Table 4).

When relevant factors were analyzed in multivariate analysis, the age at Kasai operation and bilirubin normalization at 2 months post-operation were independent risk factors affecting post-Kasai procedure survival. Patients who received Kasai operation later than 60 days after birth were more likely to experience treatment failure when compared to those who received Kasai operation before 60 days (HR 2.90, $p = 0.033$). Patients who did not experience normalization of bilirubin at 2 months post-operation were more likely to have treatment failure when compared to those who did (HR 9.89, $p = 0.002$, Table 4).

Discussion

Although many pediatric surgeons still strive for ways to improve the outcome of BA patients following Kasai operation, long-term survival with the native liver of BA patients remains below 50 % at 20 years [3]. Although there has been slight improvement in post-Kasai operation survival, it is generally conceived that not much more

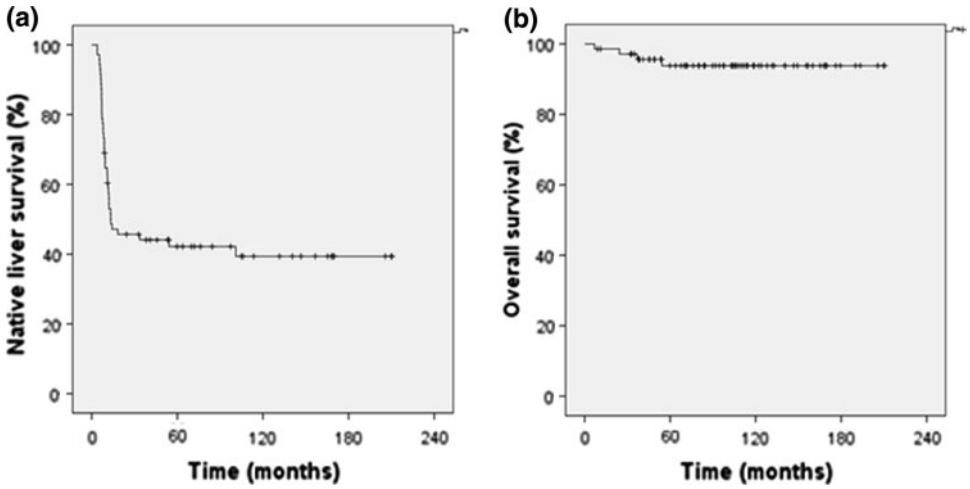

Fig. 2 Survival of patients with biliary atresia: (**a**) survival with native liver, and (**b**) overall survival

Table 4 Univariate and multivariate analysis of the prognosis factors for patient survival with native liver after Kasai operation (cox proportional hazard model)

	Univariate analysis		Multivariate analysis		
	HR	*p* value	HR	95 % CI	*p* value
Age at Kasai operation					
≤60 days	4.09	0.004	2.90	1.09–7.74	0.033
>60 days					
Bilirubin at 2 months after Kasai operation					
≤1.5	3.482	0.002	9.89	2.28–42.81	0.002
>1.5					
Postoperative cholangitis					
No	1.20	0.319	–	–	–
Yes					

progress can be expected in the future. In a nationwide survey of 435 Korean BA patients between 2000 and 2010, different methods of post-Kasai management did not result in significant differences in patient outcome (unpublished data). Kasai operation has been and still remains the most effective treatment option for BA patients. However, LT has also proved to be an important option of rescue therapy for patients who have failure of Kasai operation. In this study of 72 patients treated for BA at a single center, survival with the native liver following Kasai operation was 46.4 % at 10 years. However, by incorporating LT into the treatment scheme, 10-year patient survival was 94.9 %. These findings are consistent with previous reports from various institutions describing similar gain of survival [11–13].

The median age at LT after failure of Kasai operation was 8.8 months in our cohort of 27 patients. Except for one patient who received LT at age 8 due to recurrent cholangitis, 26 out of 27 patients experienced progression of biliary cirrhosis and went on to receive LT before 24 months. However, BA is a progressive disease and liver failure beyond childhood is occasionally seen following Kasai operation. Shinkai et al. [3] have reported that while the native liver survival after Kasai operation was 44 % at 20 years, the incidence of cirrhosis was 49 % among these patients. Moreover, beyond the age of 20, 14 % of these native liver-survivors received LT and 6 % progressed to liver failure and died. Similar findings are observed in our cohort: out of the 24 survivors with native livers after Kasai operation still being followed, 62.5 % have abnormal liver function tests, 75 % have ultrasonographic evidence of biliary cirrhosis, and 58.3 % exhibit complications pertaining to cirrhosis and portal hypertensive such as esophageal varices or splenomegaly associated with thrombocytopenia. This trend is maintained in patients both younger and older than 10 years of age. It can be said that in long-term survivors of BA after Kasai operation, a fraction of patients retain normal liver function, while the rest of the patients are in a state of compensated liver cirrhosis. A number of events may cause transient compromise in liver function, which may lead to decompensation and finally, liver failure. In this regard, long-term regular follow-up of BA patients after Kasai operation is required to assess the need for LT in these patients. Although concerns about long-term complications of LT still remain in pediatric patients, a survival rate close to 95 % at postoperative 10 years should alleviate some of these worries. Thus, we believe LT should be considered during the entire span of the BA patient's life and when necessary, should be actively pursued at the earliest possible stage.

There have been several studies investigating the prognostic factors related to "Kasai failure", which is the persistence and progression of biliary cirrhosis following Kasai operation. When failure of Kasai operation is expected, these patients must be listed for LT and preparations for LT must begin. However, with the shortage of

adequate donors, death while on the waiting list is a possibility for these patients [14]. Thus, predicting the outcome of Kasai operation early in the postoperative period is important for the clinician to make the decision to proceed with LT before liver failure becomes imminent. The disappearance of jaundice after Kasai operation has been reported in several studies to be an important factor affecting outcome [1, 8, 15, 16]. In the present study, patients with disappearance of jaundice 2 months post-Kasai operation had significantly superior survival with the native liver when compared to patients who had persistent jaundice (HR 9.89, $p = 0.002$). The median time from Kasai operation to LT in patients with failure of Kasai operation in this study was 6.2 months. Jaundice at post-operative 2 months may be an important predictive factor for Kasai operation failure and the need for LT in the upcoming months.

This study has limitations due to its retrospective design, and is accordingly subject to selection bias. On the other hand, its merits include the homogenous patient population made up exclusively of East Asian ethnicity and the consistency of treatment with which these patients have been managed during the study period. We present a real-world experience of surgical treatment of BA with respectable outcome over a period of 14 years.

Conclusion

In this single-center analysis of 72 BA patients, survival with the native liver was 39 % at 10 years with Kasai operation alone. The development of LT and its application in the management of BA has led to 94.9 % patient survival at 10 years. Among long-term survivors with native livers after Kasai operation, 58.3 % exhibit signs of cirrhosis and portal hypertensive complications. LT should be continuously considered during the long-term follow-up of the BA patient.

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