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Long-Term Survivors in Biliary Atresia —Findings for a 20-year Survival Group

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SHIMIZU, Y., HASHIMOTO, T., OTOBE, Y., UEDA, N., MATSUO, Y. and MANABE, T. *Long-Term Survivors in Biliary Atresia—Findings for a 20-year Survival Group.* Tohoku J. Exp. Med., 1997, **181** (1), 225-233 —— Recently, there has been remarkable increase in the survival rate in cases of biliary atresia (BA). However, long-term survivors are as yet a small population. Of the total of 152 patients undergoing surgery for BA during the period from 1969 to 1995 in our institution, 39 of them were operated on more than 20 years ago with follow up for all but one of these, who can no longer be accounted for. Six are still alive, 1 male, and 5 females, two cases being of type I BA, and the other 4 of type III and 1 is unaccounted for. The prognosis of these individuals was clinically evaluated. At the present time, none of them is receiving hospital care, but 3 have experienced sequelae. Two patients required partial splenic embolization (PSE), endoscopic infusion sclerotherapy (EIS), and/or gastroesophageal decongestion and splenectomy (Hassab's operation) (Hassab 1967) for hypersplenism and/or portal hypertension. The other has needed hospital care for recurrent cholangitis. Laboratory investigations revealed a serum total bilirubin (TB) of less than 1.0 mg/100 ml in 3 of the 5 patients for which samples could be obtained, between 1.0 and 2.0 mg/100 ml in 1, and in excess of this in the remaining case. The l-alanine 2 oxoglutarate aminotransferase (ALT) level was within the normal range in only 1, and was mildly to moderately elevated in 4. The white blood cell count (WBC) was less than 3,000/μl and the platelet count was less than $10\times10^4/\mu$l in 1, and within the normal ranges in the other 4 patients. The results thus indicate that occult and progressive liver damage may occur in long-term survivors of BA. —— biliary atresia; Kasai operation; long-term survivors; sequelae; prognosis

Recently, a remarkable increase has been achieved in the rate of survival without jaundice after the Kasai operation for BA (Kasai and Suzuki 1959; Kasai et al. 1968; Ohi et al. 1985). However, long-term survivors as yet constitute only

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a small population, and sequelae have been reported in many cases (Akiyama et al. 1986; Ohi et al. 1990a; Chiba et al. 1992; Tsuchida et al. 1994), such as gastrointestinal bleeding due to portal hypertension, hypersplenism, hepatopulmonary syndrome, and cystic dilatation of the intrahepatic bile ducts. This indicate that the true prognosis of BA is unclear. To cast light on this problem we performed a clinical review of individuals still alive more than 20 years after undergoing operations in our institution.

Materials and Methods

A total of 152 cases of BA were encounted during the period from 1969 to 1995 in our institution (Table 1). Thirty-nine of these were operated on more than 20 years ago. Their mean age at the time of operation was 86.7 days (range 41 to 155 days), 16 being male, and 23 female. The BA was of type I in 3, of type II in 1, and of type III in 35 cases, according to classification based on cholangiographic studies (Hashimoto and Yura 1981). Hepatic duct enterostomy could be performed in 2 of the 3 patients with type I BA, whereas the remaining 37 cases were of uncorrectable type, necessitating a Kasai operation.

Of the study group of 39 patients, 1 case who had been followed for more than 20 years could no longer be accounted for, leaving 6 survivors, constituting 15.4% of the total, available for study. Their age range is from 21 to 26, one is male, and 5 are female (Table 2). Their clinical status, was determined by personal interview. Two patients have been periodically seen in our outpatient clinic, another has been in Hawaii for the last several years, but could be reached by facsimile, and the remaining 3 were followed in other institutions. Morphological and laboratory examinations were also performed. Serum total bilirubin (TB) and ALT were measured for estimation of their liver function, and WBC and platelet counts were examined as indicators of hypersplenism and/or portal hypertension.

The survivors were divided into 2 groups: one having any kind of sequelae

Table 1. *Biliary atresia patients*

	1969-1995	1996-1976.3 (>20 years)
Cases	152	39
Male : Female	64 : 88	16 : 23
Age at operation	79.3±28.3 (range 41-189)	86.7±26.6 (range 41-155)
Type of atresia		
I	10 (4)[a]	3 (2)[a]
II	4	1
III	138	35
Survivors	75[b]	6

[a]correctable type; [b]except LTx patients.

TABLE 2. *Long-term survivors in biliary atresia* (more than 20 years)

Case	Age at present (years)	Sex	Type of atresia	Age at operation (days)	Operative procedure
1	26	M	III, c1, γ	136	Kasai operation
2	25	F	I, cyst	65	Hepatic duct enterostomy
3	24	F	III, b1, β	78	Kasai operation
4	24	F	III, a1, μ	75	Kasai operation
5	21	F	III, d, μ	84	Kasai operation
6	21	F	I, cyst	82	Hepatic duct enterostomy

during the recent part (Group 1), and the other without sequelae (Group 2). Whole body computerized tomography (CT) and/or magnetic resonance imaging (MRI) studies had been performed on the 3 patients of Group 1. From the information gained, clinical features of the long-term survivors were evaluated.

RESULTS

The 6 patients were equally divided, with 1 type I and 2 type III cases in each group (Table 3). The mean age at the operation was 86.7 days (group 1, 78, 82, and 84 days, and group 2, 65, 75, and 136 days) (Table 2).

At the present, none of the 6 is receiving any hospital care.

The sequelae experienced by patients of Group 1 were as follows (Table 3). One 24 year-old female suffered recurrent cholangitis 2 years ago. CT imaging revealed dilatation of the left intrahepatic biliary duct (IHBD) and segmental atrophy of the lateral segment of the liver (Fig. 1).

The second case, a 21 year-old female, was hospitalized for gastrointestinal bleeding last year. CT images revealed atrophy of the right liver lobe, dilatation of IHBD, and splenomegaly (Fig. 2). Gastrointestinal fiberscopy (GIF) revealed gastroesophageal varices with red color signs. EIS and PSE were performed for portal hypertension and hypersplenism, but she suffered recurrent gastrointestinal bleeding. Therefore, she had to undergo Hassab's operation.

The remaining case is a 21 year-old female who has frequently suffered from

TABLE 3. *Sequelae and treatments*

Case	Sequelae	Treatment	Group
1	None	—	2
2	None	—	2
3	Ascending cholangitis	Conservative treatment	1
4	None	—	2
5	Jaundice, hypersplenism	PSE	1
6	Hypersplenism, gastroesophageal varices	PSE, Hassab's operation	1

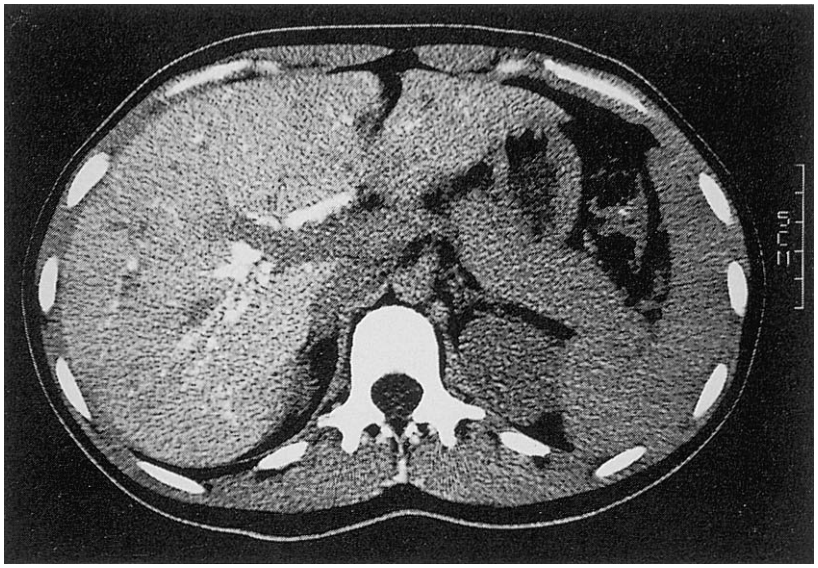

Fig. 1. A 24 year-old female who suffered recurrent cholangitis 2 years ago. CT imaging revealed the dilatation of the left intrahepatic bile duct (IHBD) and a stricture at the anastomotic site.

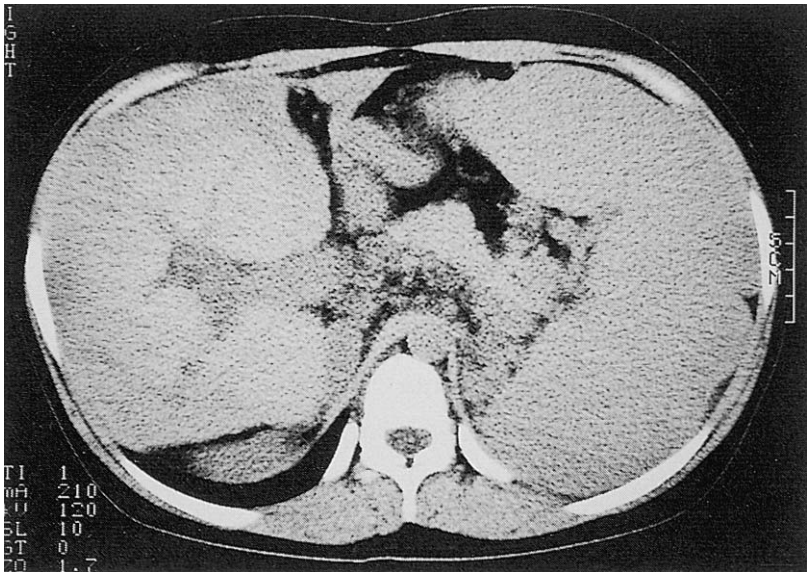

Fig. 2. A 21 year-old female who was hospitalized for gastrointestinal bleeding last year. The images revealed remarkable atrophy of posterior and lateral segment, mild dilatation of IHBD, and prominent splenomegaly.

recurrent cholangitis, jaundice, and/or gastrointestinal bleeding from esophageal varices (Fig. 3). Recent CT images revealed remarkable atrophy of the posterior and lateral segments, mild dilatation of IHBD, and prominent splenomegaly (Fig. 4). Esophageal varices were shown by GIF. Her hypersplenism and portal hypertension were treated by PSE, but the results of laboratory examination showed hypersplenism and jaundice (Table 4). The necessity of a liver transplantation in the near future is indicated.

The three patients of group 2 were found to be subjectively healthy without

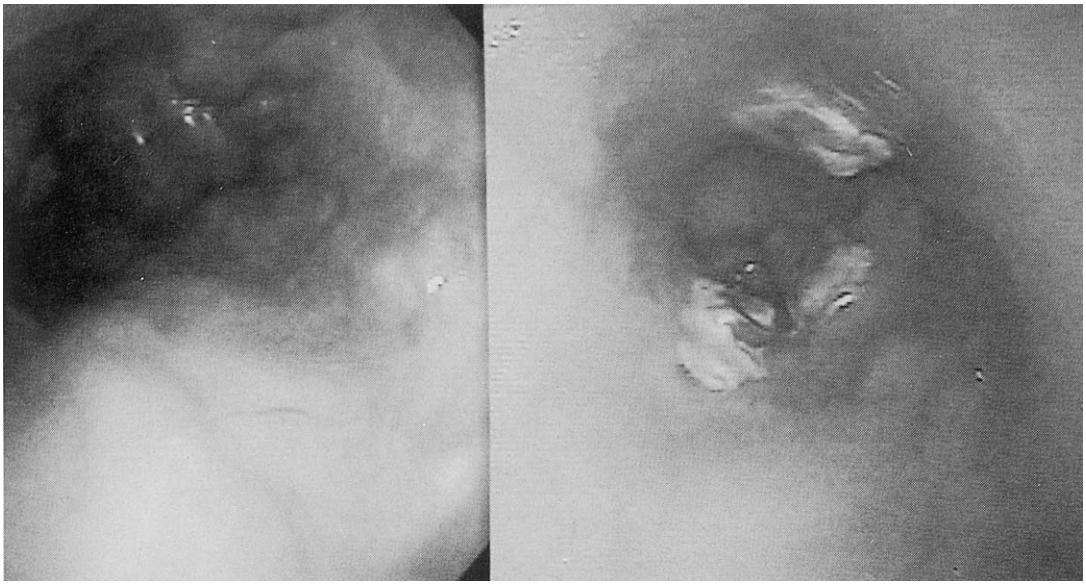

Fig. 3. Gastrointestinal fiberscopy revealed gastroesophageal varices with red color sign. EIS and PSE were performed for portal hypertension and hypersplenism, but she suffered recurrent bleeding. Therefore, we performed Hassab's operation.

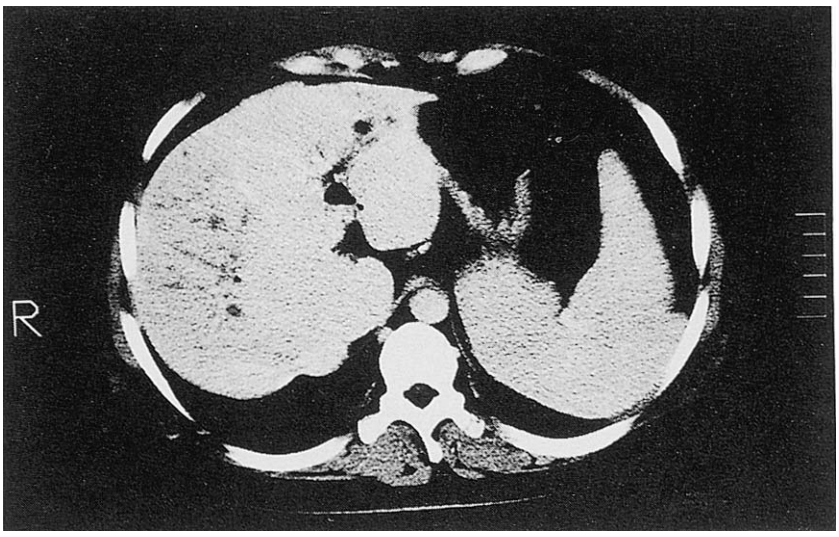

Fig. 4. A 21 year-old female who frequently suffered from recurrent cholangitis, jaundice, and/or gastrointestinal bleeding from esophageal varices. CT images revealed atrophy of the right liver lobe, dilatation of IHBD, and splenomegaly.

any problems, and living normal lives.

Five patients underwent laboratory examinations. The remaining one patient not available to take samples because she has been in Hawaii for several years. The results of the laboratory investigations were as follows (Table 5); The serum ALT level of 1 patient in Group 2 was in the normal range (<30 U/liter), but 2 patients in Group 2 demonstrated mild abnormality (between 30 and 100 U/liter), and 2 in Group 1 had moderate elevation (>100 U/liter). The WBC was

TABLE 4. *Results of laboratory examinations* (Case 5)

WBC	2,500/μl	TB	3.5 mg/100 ml	ALP	871 U/liter
RBC	$403\times10^4/\mu$l	DB	2.6 mg/100 ml	GGT	242 U/liter
Hb	12.2 g/100 ml	TP	6.8 g/100 ml	LAP	157 U/liter
Ht	36.7%	Alb	4.0 g/100 ml	AST	90 U/liter
Plt	$4.4\times10^4/\mu$l	ZTT	11.7 kU	ALT	59 U/liter
		TTT	20.5 kU	LDH	175 U/liter
		choE	110 U/liter	Bile acids	245.9 μmol/liter
		T chol	276 U/liter		

TABLE 5. *Results of laboratory investigations* (1996.3)

Case	TB (mg/100 ml)	ALT (U/liter)	WBC (/μl)	Plt ($\times10^4/\mu$l)	Group
1	0.7	142	5700	17.1	2
2	1.7	119	4800	11.6	2
3	0.6	34	5200	28.6	1
4	—	—	—	—	2
5	3.5	59	2500	4.4	1
6	0.5	20	7900	29.3	1

Patient #4 is known to be healthy from personal communication.

less than 3,000/μl and the platelet count was less than $10\times10^4/\mu$l in one patients in Group 2. Values were within the normal ranges in the other 4 patients.

DISCUSSION

Of the total of 152 cases in our series, all those with correctable type BA are still alive, whereas only 10.8% of patients with uncorrectable type BA have survived. However, while the classification of atresia correlated with the prognosis, there was no absolute association regarding sequelae since one individual with type I BA was found in our present group 1.

Ohi et al. (1990b) have suggested that an early Kasai operation leads to a better prognosis, but this has been disputed by Toyosaka et al. (1993). In our series, the mean age at the initial surgery in Group 1 was greater than in Group 2, but in all cases it was later than 60 days after birth. Whether there have been rare long-term survivors because of deficiencies in early operations remains unclear. However, development of portal hypertension has been described as a feature of long-term survival, despite evidence of restoration of bile flow (Saeki et al. 1986; Ohi et al. 1986). Our 6 patients also remained without jaundice for a long time and in good general condition after Kasai operation. The 3 patients

with sequelae, had episodes of ascending cholangitis and/or bleeding from gastroesophageal varices at the ages of 18, 21, and 22. They had not complained of any problems in their daily life before the sudden onset of new symptones, but portal hypertension has now developed in 2 of them. The 50% incidence in our series is in line with Toyosaka's report where 61.9% of patients followed for more than 10 years after surgery for BA had a history of late complications (Toyosaka et al. 1993). Varying degrees of liver dysfunction persisted in about half of their long-term survivors, although there were no clinical problems observed in two thirds of survivors in the series of Kasai et al. (1985) and Akiyama et al. (1986). Therefore we consider that long-term follow up is important, even if patients do not complain of any symptoms over long periods. When a patient with BA has an episode of bleeding due to portal hypertension, we usually attempt EIS, PSE, splenectomy (as part of Hassab's operation), shunt operations, or conservative treatment. Most gastroesophageal varices can be well managed with EIS (Soehendra 1982), but in one of our patients Hassab's operation was necessary to control severe bleeding from varices in stomach and hypersplenism. Another patient has remained hypersplenic in spite of PSE. Toyosaka et al. (1993) reported that surgical treatment should be restricted to older children with severe hypersplenism who are resistant to sclerotherapy. We also prefer PSE to splenectomy for hypersplenism, because of the resulting high risk of overwhelming sepsis with the latter (King and Shumacker 1952; Evans 1985; Hashimoto et al. 1989). However, it is a fact that patients who have severe portal hypertension sometimes require surgical treatment.

In our series, despite the lack of subjective problems, evidence of cirrhosis and/or slight portal hypertension was obtained. This is in line with another report describing agreement with other of BA survivors having some abnormalities in morphological examination, including cirrhosis, portal hypertension, IHBD, and hepatic ischemia (Day et al. 1989).

With regard to indications for liver transplantation, Kasai et al. (1987). reported that cases with mild jaundice (serum TB lower than 5 mg/100 ml) have a possibility of improvement in their condition, and are not recommended for liver transplantation. However, with BA long-term survivors who are more than 20 years old, the present results suggest that we must take liver transplantation into consideration. For example, in the case with the most prominent liver damage in our present series, it is clearly indicated.

The fact that the ALT results were worse for Group 2 than Group 1, and the serum TB level was within the normal range in 2 Group 1 cases is compelling evidence that occult and progressive liver damage can occur in long term survivors, even when without apparent cholangitis. Thus it is very important that such individuals be followed up carefully, irrespective of whether they complain of any problems.

Conclusion

In our series, there are 6 survivors of Kasai operations aged 21 to 26 years old, were investigated. Despite being asymptomatic, laboratory findings revealed some abnormalities indicative of progressive liver damage.

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