Tohoku J. Exp. Med., 1997, **181**, 175-183

Further Observations on Cystic Dilatation of the Intrahepatic Biliary System in Biliary Atresia after Hepatic Portoenterostomy: Report on 10 Cases

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KAWARASAKI, H., ITOH, M., MIZUTA, K., TANAKA, H. and MAKUUCHI, M. *Further Observations on Cystic Dilatation of the Intrahepatic Biliary System in Biliary Atresia after Hepatic Portoenterostomy: Report on 10 Cases.* Tohoku J. Exp. Med., 1997, **181** (1), 175-183 —— This is a report on ten patients with cystic dilatation of the intrahepatic biliary system (CDIB) after hepatic portoenterostomy. They were five girls and five boys and the diagnosis of CDIB was made at ages 6 months to 11 years (mean age: 2.8 ± 3.3 years). Follow-up ranged from one month to 15 years (mean: 5.5 ± 4.9 years). In order to elucidate the factors which affect the clinical outcome of such patients, the types of CDIB (Type A: non-communicating solitary cyst, Type B: communicating solitary cyst, Type C: multi-cystic dilatation), clinical symptoms at onset of CDIB and the method for the treatment were reviewed in relation to the outcome. For the purpose of understanding pathogenesis of CDIB, immunohistochemical study on hepatobiliary system was done with monoclonal antibody for cytokeratin. Outcome of the patients of Type C was poor, whereas the outcome of patients with type A and B was good. The outcome of preoperatively jaundiced patients was poor, but jaundice-free patients showed good outcome. Method of treatment was not related to the outcome. As epithelium of CDIB was positive for monoclonal antibody of cytokeratin, it was suspected that pathogenesis of CDIB might be related to peribiliary gland which originated from ductal plate. ———— biliary atresia; dilatation of the intrahepatic bile ducts; Kasai's operation

Cystic dilatation of intrahepatic biliary system (CDIB) has been observed with increasing frequency in proportion to increasing number of long-term surviving patients with biliary atresia after Kasai's operation (Kasai et al. 1968). Danks and Campbell (1966), in their original study, believed that these lesions

Received June 30, 1996; revision accepted for publication November 15, 1996.

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This paper was presented at 6th International Sendai Symposium on Biliary Atresia, May 20 and 21, 1996, Sendai.

were potentially operable and could be drained into the intestine by direct surgical anastomosis. On the other hand, Fonkalsrud and Arima (1975) suggested that these cysts occur in biliary atresia only beyond the age of 3 months once irreversible hepatic damage appears. As shown in the above two representative reports, proper treatments for this disease has not yet been formulated and pathogenesis has not been clarified. The purpose of this paper is to report 10 patients with CDIB and elucidate the proper treatments and pathogenesis by clarifying factors which affect the outcome of patients with CDIB.

Patients and Methods

Eighty three patients with biliary atresia (BA) were operated on and 5 patients who had been operated on at the other institution under the same surgical procedure as ours were admitted for the postoperative care between January 1971 and May 1996 at the University of Tokyo Hospital. CDIB after Kasai's operation was observed in 10 (11.4%) out of 88 patients. Diagnosis of CDIB was done by ultrasonography and confirmed by percutaneous transhepatic cholangiography (PTC) or intra-operative cholangiography in all of ten patients. They were five girls and five boys and the diagnosis of CDIB was made at ages 6 months to 11 years (mean age: 2.8 ± 3.3 years) (Table 1). Follow-up ranged from one month to 15 years (mean age: 5.5 ± 4.9 years). First three patients (Case 1 to 3) had been already reported in the other paper (Tsuchida et al. 1994) and further follow-up of these three cases was reviewed with the report of additional seven new cases in this paper. In order to elucidate the proper treatment of this disease, background factors which were suspected to be correlated to the clinical outcome were analyzed. As background factors, types of CDIB, symptoms at onset of CDIB and methods for treatment of CDIB were analyzed in relation to the clinical outcome. The clinical outcome of the patients with CDIB were evaluated to be "good" when CDIB disappeared without any complications and to be "poor" when CDIB persisted or complications such as fever, jaundice and right upper abdominal pain were associated with CDIB. Outcome of the patient in whom liver transplantation was performed was categorized to be poor.

Types of CDIB were consisted of Type A; non-communicating solitary cyst, Type B; communicating solitary cyst and Type C; multi-cystic dilatation (Tsuchida et al. 1994) (Fig. 1). The classification was primarily based upon the shape of the intrahepatic biliary system of the patients with CDIB. When two different types of cysts were observed simultaneously in one patient, classification of the cyst was made by more advanced type of cyst. Type C was considered most advanced because of the augmented numbers of cysts (Fig. 2) compairing to the other Types. During percutaneous transhepatic bile drainage (PTBD) for the patients of Type A(Fig. 3A), communication between the cyst and surrounding intrahepatic biliary system appeared (Fig. 3B). And so, Type A was considered to be second and Type B to be third advanced.

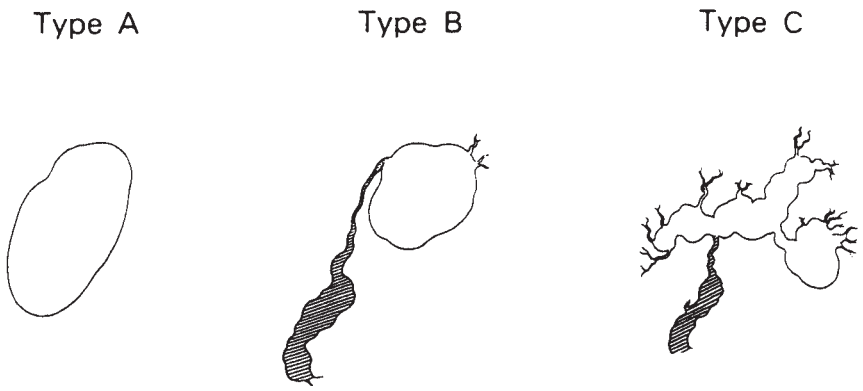

Fig. 1. Classification of Types of CDIB: Type A-non-communicating cyst, Type B-cyst communicating with the intestinal loop, Type C-multi-cystic dilatation.
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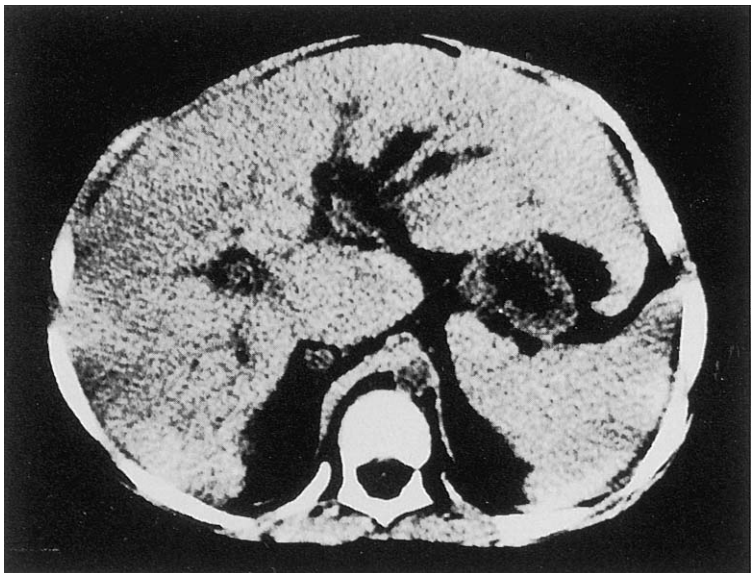

Fig. 2. CT scan of the liver of Case 6.
Type C, multi-cystic dilatation of CDIB.

Symptoms at onset of CDIB were fever and jaundice which were associated with ascending cholangitis generally seen in the 35% of the patients with BA after hepatic portenterostomy in Japan following the report of nation wide annunal registration of BA (The Japanese Biliary Atresia Society 1995).

Treatments of CDIB were consisted of PTBD, revision of hepatic portoenterostomy and liver transplantation.

Statistical study was done by Fisher tests and $p<0.05$ was considered as significant difference

Histochemical study with monoclonal antibody for cytokeratin was performed on the liver specimen taken at liver transplantation of Case 4, 7 and 9. Those specimens were fixed in 4% formaldehyde and embedded in paraffin, then

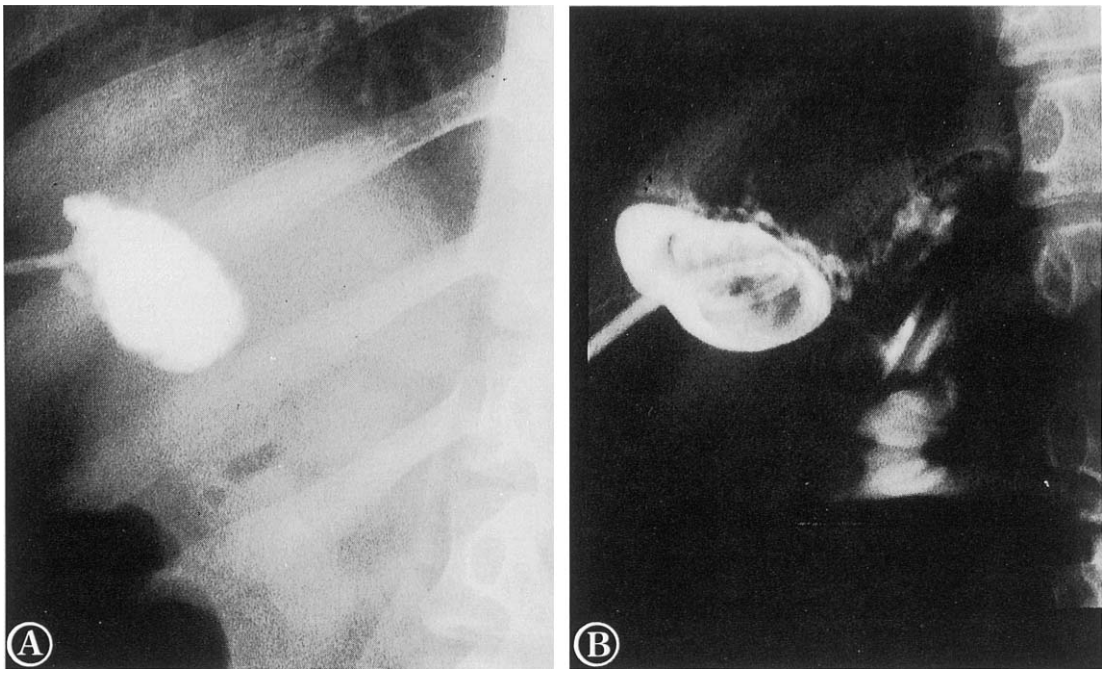

Fig. 3A. PTC of Case 7. Type A, CDIB without communication
Fig. 3B. PTC of Case 7, five weeks after Fig. 3A
Type B, with tiny communication with the intestinal loop.

followed by avidin-biotin-peroxidase complex method of Hsu et al. (1981). The epithelium of CDIB was examined whether it is positive for monoclonal anti-cytokeratin antibodies CAM 5.2 and AE1 (Van Eyken et al. 1988).

Results

In Cases 2 and 3, two different types of cysts were found. One Type A cyst and one Type B cyst were found simultaneously in Case 2 who was classified to Type A, following the above mentioned reason. Case 3, in whom a Type A cyst was found first and Type C at autopsy, was classified to Type C for the same reason.

The correlation between the outcome of the patients with CDIB and the following three factors were analyzed (Tables 1 and 2).

Type of CDIB. After treatments, cysts disappeared and no associated complications were observed in all of the four patients of Type A and B. On the other hand, two died, three were transplanted liver and the rest one patient has been admitted in our hospital and PTBD has been continued for these two months. Type C cysts are still observed in this patient. Outcome of Type A and B was significantly better than that of Type C ($p<0.05$).

Symptoms of CDIB. Fever was observed in all of the ten patients. On the other hand, jaundice was observed in 100% (6/6) of the patients in Type C whose outcomes were poor, and no jaundice was shown in the patients of Type A and B whose outcomes were good. Rate of occurrence of jaundice was significantly lower in the patients of good outcome than in those of poor outcome ($p<0.05$).

TABLE 1. *Profile of the 10 patients with CDIB*

Case	Sex	BA Type	CDIB Type	Onset		Treatments	Outcome	Current age
				Age	Symptoms			
1	M	Icβ	A	1 y	F	RV	Good	16y8m
2	F	Icβ	A	9 m	F	PTBD	Good	13y6m
3	M	IIIbβ	C	3 y	F, J	None	Died	(9y11m)
4	F	Icβ	C	7 y	F, J, C	PTBD, RV→LTX	Poor	17y3m
5	M	IIIbν	A	11 y	F	PTBD	Good	14y1m
6	F	IIIbμ	B	9 m	F, C	RV	Good	7y7m
7	M	IIIaν	C	3 y	F, J, C	None→LTX	Poor	6y2m
8	F	IIIbν	C	7 m	F, J	None	Died	(8m)
9	F	IIIbν	C	6 m	F, J	None→LTX	Poor	1y2m
10	F	IIIbμ	C	8 m	F, J	PTBD	Poor	1y5m

F, Fever; J, jaundice; C, cholangitis; PTBD, percutaneous transhepatic bile drainage; RV, revision of hepatic portoenterostomy; LTX, liver transplantation.

TABLE 2. *Type of CDIB, symptoms, treatments and outcome*

Outcome	Types			Symptoms at onset		Treatments		
	A	B	C	Icteric	Anicteric	PTBD	RV	None
Good	3	1	0	0	4	2	2	0
Poor	0	0	6	6	0	2	1	4

PTBD, percutaneous transhepatic bile drainage; RV, revision of hepatic portoenterostomy.

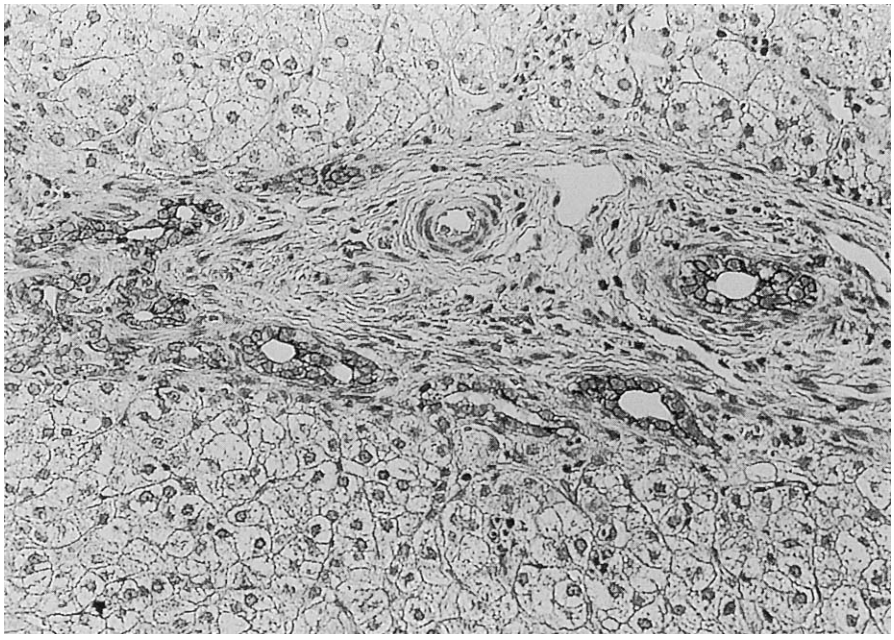

Fig. 4. The epithelium of CDIB of Case 9 is positive for monoclonal anticytokeratin antibody CAM 5.2.

Treatment of CDIB. Revision of the hepatic portoenterostomy was performed in each one of Type A and B with success and in one of Type C without success. PTBD was performed in two of Type A with success and in one of Type C without success. Method of treatment did not seem to be related to the outcome of CDIB, but statistical examination could not be completed because of lack of number.

Histochemical study for cytokeratin. Epithelium of CDIB of Cases 4, 7 and 9 (Fig. 4) were all positive to both CAM 5.2 and AE1. Interestingly, some hepatocytes of Case 7 were also positive for CAM 5.2.

DISCUSSION

There had been several reports on the association of intrahepatic cysts or bile lakes with biliary atresia which were found at autopsy (Danks and Campbell 1966; Suruga et al. 1967; Fonkalsrud and Arima1975; Fain and Lewin 1989) and experiences with CDIB in postoperative patients with BA were reported by

Kimura et al. (1980), by Ito et al. (1983) and by Saito et al. (1984). Some authors thought CDIB can be drained surgically (Danks and Campbell 1966; Ando et al. 1988) but the other believed it cannot be cured by surgical anastomosis (Fonkalsrud and Arima 1975; Fain and Lewin 1989; Chiba et al. 1992). Chiba et al. (1992) noted what we call Type C intrahepatic biliary dilatation in three postoperative patients with BA and concluded that such irregular dilatation appears to predispose the patient to further episodes of cholangitis and irreversible liver cirrhosis. Fain and Lewin (1989) reported intrahepatic biliary cysts in BA and believed that the intrahepatic cysts are an acquired phenomenon that appears later during the course of BA and surgical drainage is unlikely to be effective. In our series of six patients with Type C dilatation, two died and the other three had to undergo LTX; only one is alive without LTX. These results coincide with the report of Chiba and his associates in general tendency.

Ando and his associates (Ando et al. 1988) reported that a tiny communication between CDIB and the intestinal loop (Type B) appeared after PTBD in three cases of Type A cyst which had no communication before PTBD and a couple of years after repeated PTBD, CDIB disappeared in these three cases. In our series, a tiny communication from CDIB to the jejunal loop was shown five weeks after PTBD on Type A cyst in Case 7 and CDIB disappeared two months after PTBD. Also in Case 2, CDIB disappeared and no complications were observed. These two Type A cases of our series were successfully treated with PTBD like Ando's report.

It was shown that type of CDIB and symptom at the onset of CDIB were correlated to the outcome of the patients with CDIB. It is mandatory to find CDIB in early stage before any pathological changes in the liver develop irreversibly shown in Type C. Regular check-up with ultrasonography is necessary for early diagnosis of CDIB in the postoperative patients with BA at the stage of Type A or B. Once CDIB will advance to Type C in which pathological changes of the liver are cirrhotic, any treatments except liver transplantation are not effective from out results. Terada and Nakamura (1993) reported that biliary cells began to bud from the ductal plate into the mesenchyme at 10 weeks gestation and formed double-layered cord which had transformed completely into tubules by 30 weeks. The tubules gradually increased in number and aggregated to form immature peribiliary gland which increase in number and reached mature peribiliary gland by 15 years. Developing and developed peribiliary gland were positive for monoclonal anticytokeratin antibodies AE1 and CAM 5.2. From our results of immunohistochemistry of CAM 5.2 and AE1, it can be considered that cyst of Type C might be originated from peribiliary gland.

Shah and Gerber (1989) reported that the hepatocytes before 36 weeks of gestation are positive for AE 1 but not positive after that period. The findings for some hepatocytes of Case 7 to be positive for AE1 suggests the possibility of retrograde differentiation of hepatocytes of the patients of CDIB. But the

number of positive hepatocytes are too small to get a conclusion of this theory. More study is needed to verify this conclusion.

Conclusions

1. Further follow-up of three patients who had been already reported and clinical course of additional new seven patients of CDIB were reported.

2. Clinical outcome of CDIB is related to Type of CDIB and symptoms at the onset of CDIB. Outcome of the treatment of CDIB is good in the patients of Type A ($n=3$) and B ($n=1$), but poor in the patients of Type C ($n=6$). Although the four patients of Type A and B were anicteric, all of six patients of Type C were icteric at the onset of CDIB.

3. Proper treatment for CDIB is to find it in early stage by regular check up of ultrasonography and perform PTBD or revision of hepatic portoenterostomy. Once CDIB advance to Type C and the patient is committed to end stage liver failure, liver transplantation will become necessary.

4. Pathogenesis of CDIB is not clear yet but the cyst of Type C may originate from peribiliary gland.

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