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Japanese Biliary Atresia Registry, 1989 to 1994

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IBRAHIM, M., MIYANO, T., OHI, R., SAEKI, M., SHIRAKI, K., TANAKA, K., KAMIYAMA, T. and NIO, M. *Japanese Biliary Atresia Registry, 1989 to 1994.* Tohoku J. Exp. Med., 1997, **181** (1), 85-95 —— The Japanese Biliary Atresia Society founded in 1980 for the aim of investigations of all aspects of biliary atresia (BA), started a nationwide registry of BA patients in 1989. A total of 626 cases were registered from 1989 to 1994. The male to female ratio was 0.58. Corrective surgery was performed in 603 patients. Regarding the type of obstruction, 63 cases were Type I, atresia of the common bile duct, 9 were Type II, atresia of the hepatic ducts, and 543 were Type III, atresia of the porta hepatis. As initial corrective procedures, original Roux-en Y, Suruga II and Roux-en Y with intestinal valve were mainly employed. Jaundice cleared in 346 patients (57%) and decreased in 131, while it persisted in 120. The 5-year-follow-up showed that 34 patients, 49% of the patients who were followed up, were alive without jaundice, while 28 (41%) are dead. Thirty five, 33% of the patients who were entered to the Registry, were lost to follow-up. —— biliary atresia; registry; Japan

The short-term results of surgery for biliary atresia (BA) have markedly improved. However, the etiology is still unknown and the long-term efficacy of hepatic portoenterostomy remained controversial. The Japanese Biliary Atresia Society founded in 1980 for the aim of investigations of all aspects of BA, started a nationwide registry of BA patients (The Japanese Biliary Atresia Registry, JBAR) in 1989 (Chiba 1991). Department of Pediatric Surgery of Tohoku University School of Medicine was nominated to be the registration center. Data sheets were collected from institutions throughout Japan in each year for 6 years from 1989 to 1994. We analyzed the collected data of 626 patients with BA and presented the results in this paper with the approval of the society committee.

MATERIALS AND METHODS

JBAR consisted of an initial questionnaire and a follow-up questionnaire.

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The initial questionnaire is designed to obtain family history, gestational and perinatal history, associated anomalies, diagnostic methods, age at operation, type of pathological anatomy, surgical procedures, post operative management, post operative course and short-term results. The patients once registered are required to be reported every year in the registry by the follow-up questionnaire including late results of treatment, the further surgical treatment such as revision of Kasai procedure and liver transplantation, complications including portal hypertension and the mental and physical development of the patients.

Results

Data sheets were collected from 43, 48, 53, 39 and 52 institutions throughout Japan in each year for 6 years from 1989 to 1994. From 1989 to 1994 a total of 626 cases were entered into the Registry. Among them 603 underwent corrective surgery. Only during 1994, a total of 107 cases were registered and 105 of them received the operation.

Sex

The registry showed that 227 patients were males and 390 were females with the sex of 8 patients not reported. The sex ratio showed a female to male predominance of 1 : 0.58

Gestational and perinatal history

An abnormal pregnancy was reported in 145 cases (23%). There were 33 cases of toxemia of pregnancy, 27 cases of threatened abortion, 21 cases of anemia, 30 cases of other conditions and 23 cases with unidentified conditions. Smoking during pregnancy was reported in 40 cases (6.4%). Regarding the gestational age, the majority of cases were within the age range of 36–41 weeks (Table 1). Birth weight ranged from 2,500 g to 4,000 g and only 19 cases (3%) weighed less than 2,500 g at birth (Table 2). Neonatal bleeding occurred in 50 patients (8%).

Associated congenital anomalies

A total of 152 associated anomalies were observed in 114 cases (18.7%) including cardiovascular anomalies in 27, splenic anomalies in 15 (polysplenia, 11; asplenia, 1; accessory spleen, 3), preduodenal portal vein in 4 and situs inversus in 6 (Table 3).

Diagnosis

While abnormal color of meconium was recognized at birth in only 89 cases (14%) yellow colored stools were observed in 369 cases (58.9%) after feeding milk. The stool color subsequently became abnormal in 579 patients by the time of admission (Table 4). The total serum bilirubin ranged from 3.2 mg/100 ml to 32.5 mg/100 ml with an average of 11 mg/100 ml. Abdominal ultrasound was the

TABLE 1. *Gestational age* (JBAR, 1989-1994)

Weeks	Number of cases	
	1994	1989～1994
～29	0	2
30～31	1	2
32～33	1	5
34～35	1	12
36～37	13	73
38～39	49	274
40～41	37	229
42～	2	10

TABLE 2. *Birth weight* (JBAR, 1989-1994)

Weight (g)	Number of cases	
	1994	1989～1994
1,000～1,499	2	5
1,500～1,999	0	4
2,000～2,499	8	8
2,500～2,999	35	224
3,000～3,499	49	251
3,500～3,999	10	67
4,000～	2	2

TABLE 3. *Associated anomalies* (JBAR, 1989-1994)

Anomaly	Number of anomalies
Cardiovascular	27
Splenic	15
Meckel's diverticulum	8
Preduodenal portal vein	4
Malrotation	3
Situs inversus	6
Urological	8
Hypogenesis of the lung	2
Umbilical hernia	33
Inguinal hernia	28
Others	18

(152 anomalies in 114 patients)

TABLE 4. *Color of stools* (JBAR, 1989-1994)

Time	Color	1994	1989～1994
At birth	Normal meconium	53	259
	Abnormal	11	89
	Not known	43	278
After feeding milk	Yellow colored	69	369
	Abnormal	20	166
	Not known	18	91
At admission	Yellow colored	7	22
	Abnormal	97	579
	Not known	3	25

most commonly used, followed by lipoprotein X, duodenal aspiration, serum bile acid, score test based on routine clinical and laboratory data and others. Using a proper combination of these investigations diagnosis can be confirmed (Fig. 1). Laparoscopy and percutaneous cholangiography were not widely employed as diagnostic measures in Japan.

Initial surgery and choleretics

Five hundred sixty four patients (90%) underwent hepatic portoenterostomy and 37 hepaticoenterostomy. Liver transplantation was not employed as a primary therapeutic modality (Table 5). The age at operation had a certain impact on bile drainage. Below 90 days of age we got maximal results while after

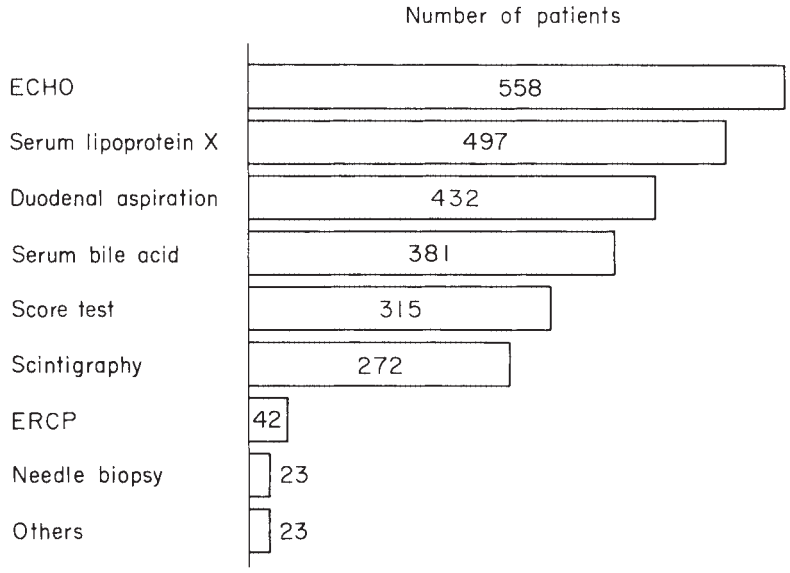

Fig. 1 Diagnostic tools used in patients registered in JBAR from 1989 to 1994 are illustrated. Abdominal ultrasound was the most commonly used, followed by lipoprotein X, duodenal aspiration, serum bile acid, score test based on routine clinical and laboratory data and others.

TABLE 5. *Initial operation* (JBAR, 1989-1994)

Procedure	1994	1989～1994
Hepaticoenterostomy	5	37
Hepatic portoenterostomy	99	564
Liver transplantation	0	0
Exploratory laparotomy	1	1
Not known	0	1

90 days the results worsened. Occurrence of cholangitis showed no significant difference with age (Table 6). To achieve good postoperative bile flow choleretics were routinely used. Ursodeoxycholic acid was the most commonly used, followed by steroid hormones, dehydrocholic acid, glucagon and others (Fig. 2). A combination of several kinds of drugs was administered in most institutions. There was no bile flow after operation in 65 cases while 532 out of 603 achieved bile flow. Jaundice cleared in 346 patients (57%) and decreased in 131, while it persisted in 55 (Table 7).

Type of obstruction

Types of obstruction based on Ohi et al. (1987) (Fig. 3) are as the following: In Type I , atresia of the common bile duct, 52 out of 63 cases, 82.5%, cleared jaundice and in Type II, atresia of the hepatic ducts, 8 out of 9 cases, 88.9%, cleared jaundice. On the other hand in Type III, atresia of the porta hepatis, only about half of the cases (284/543) showed disappearance of jaundice (Table 8). Regarding Subtypes, Subtype a, in which the distal bile duct was patent through the gallbladder to the duodenum, showed the best results with 90.6% of jaundice-clearance rate, while Subtype b, in which the distal bile duct was atretic, showed the worst prognosis. In Subgroups the results are not considerably different except for typeα, dilated hepatic ducts, in which the best results of jaundice-clearance rate (92.3%) were achieved.

TABLE 6. *Age at operation and results* (JBAR, 1989-1994)

Age at operation (days)	Number of cases	Jaundice disappearance	(%)	Cholangitis	(%)
～30	33	19	(57)	9	(27)
31～45	83	51	(61)	25	(30)
46～60	133	79	(59)	55	(41)
61～70	131	83	(63)	48	(36)
71～80	93	48	(52)	34	(36)
81～90	49	28	(57)	20	(41)
91～	93	37	(39)	38	(40)

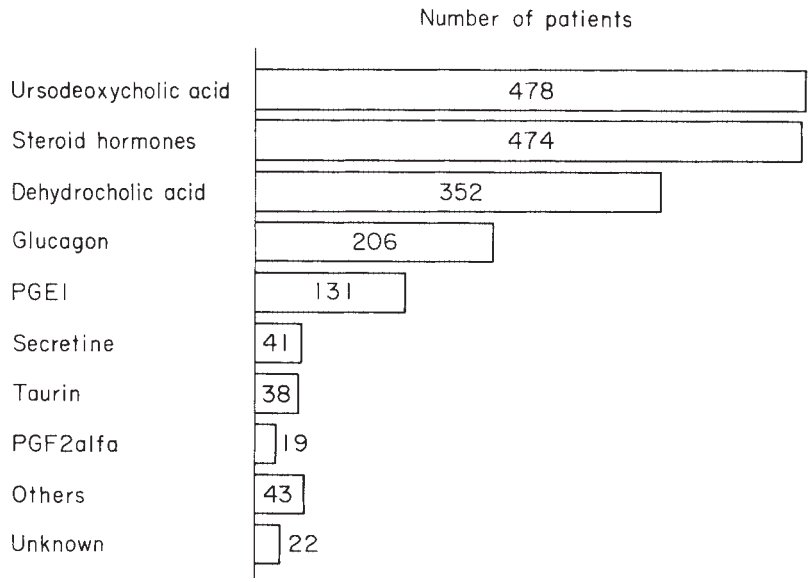

Fig. 2 Choleretic agents administered to patients registered in JBAR from 1989 to 1994 are illustrated. Ursodeoxycholic acid was the most commonly used, followed by steroid hormones, dehydrocholic acid, glucagon and others.

TABLE 7. *Bile flow after initial operation* (JBAR, 1989-1994)

Bile flow	1994	1989~1994
No	11	65
Yes		
Jaundice cleared	51	346
Jaundice decreased	27	131
Jaundice persisted	16	55
Not known	0	6
Total	105	603

Complications

In addition to common postoperative complications of abdominal surgery in 155 patients (25.7%) (Table 9), cholangitis was the most frequent and serious complication. Three hundred sixty one cases out of 603 (59.9%) suffered from this dreadful complication. In a number of operative modifications to prevent cholangitis, original Roux-en Y, Suruga II and Roux-en Y with intestinal valve were mainly employed. In terms of bile drainage, these three procedures were almost equivalent. However, original Roux-en Y seemed to show the better results than the other procedures in the incidence of cholangitis (Table 10).

Reoperation

Reoperation was performed in 186 out of 603 cases (30.8%). Portal redissection was performed in 132 cases, portal curettage in 27 and others (Table 11).

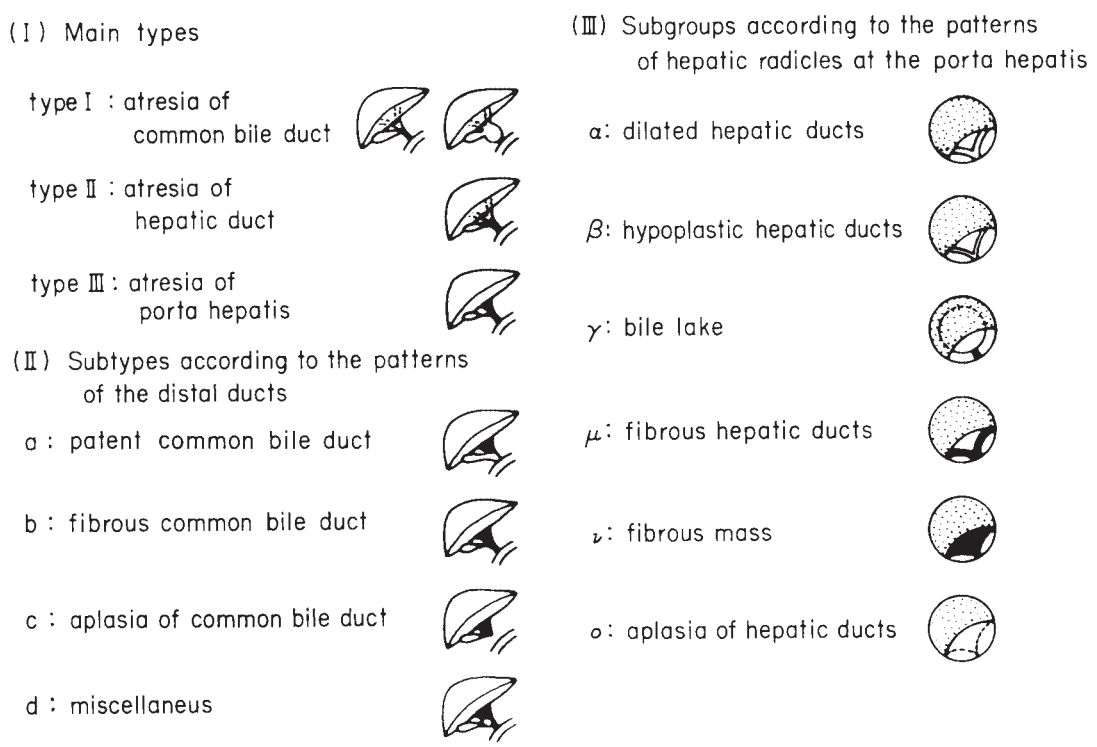

Fig. 3 The classification of type of obstruction which was established by Kasai et al is illustrated. The morphology of this disease can be classified by the macroscopic findings and direct cholangiogram in terms of 3 categories, namely, main types (I, II and III) according to the site of obstruction, subtypes (a, b, c and d) according to the patterns of distal bile ducts and subgroups (α, β, γ, μ, ν and o) according to the patterns of hepatic radicle.

TABLE 8. *Classification and results* (JBAR, 1989-1994)

Types		Number of cases	Jaundice disappearance	Cholangitis
Main Types	I	63	52	39
	II	9	8	5
	III	543	284	201
Subtypes	a	117	106	37
	b	370	201	139
	c	89	40	38
	d	18	13	8
Subgroups	α	26	24	10
	β	30	22	10
	γ	43	25	12
	μ	81	47	29
	ν	295	206	153
	o	22	12	3

TABLE 9. *Postoperative complication* (JBAR, 1989-1994)

Complication	1994	1989~1994
Ileus	4	37
Peritonitis	0	8
Bleeding	5	30
Pulmonary complication	1	9
Acute liver failure	2	14
Infection	3	21
Others	3	36
Total	18	155

TABLE 10. *Procedures and cholangitis* (JBAR, 1989-1994)

Procedure	Number of Cases	Jaundice disappearance	Cholangitis
Original Roux-ex Y	233	125	75
Hepatic portoduodenostomy	5	5	2
Suruga I	1	1	1
Suruga II	105	60	50
Double Roux-en Y	7	4	3
Sawaguchi	37	18	11
Roux-en Y with valve	166	96	64
Others	35	13	9

Regarding the preoperative history of the patients undergoing reoperation, there was no bile flow after the reoperation in 38 cases, while bile flow was achieved in 139 cases. Jaundice was cleared in 62, decreased in 37 and persisted in 40 after the reoperation (Table 12).

Outcome of 5-year-follow-up

The 5-year-follow-up showed that 34 patients, 49% of the patients who were followed up, were alive without jaundice, while 28 (41%) are dead. On the other hand 35 patients, 33% of the patients who were entered to JBAR, were lost to follow up (Fig. 4).

DISCUSSION

The goal of JBAR is to study every aspect of BA, especially epidemiology and the long-term survival of BA by accumulation of large number of cases from multiple centers.

In the United States the Biliary Atresia Registry was introduced in 1978 (Karrer et al. 1990). The patient age at operation was strongly correlated not

TABLE 11. *Reoperation* (JBAR, 1989-1994)

Procedure	1994	1989~1994
Portal redissection	27	132
Portal curettage	4	27
Endoscopic curettage	0	8
Others	7	10

TABLE 12. *Bile flow after reoperation* (JBAR, 1989-1994)

Bile Flow	1994	1989~1994
No	7	38
Yes		
Jaundice cleared	17	62
Jaundice decreased	9	37
Jaundice persisted	5	40
Total	38	177

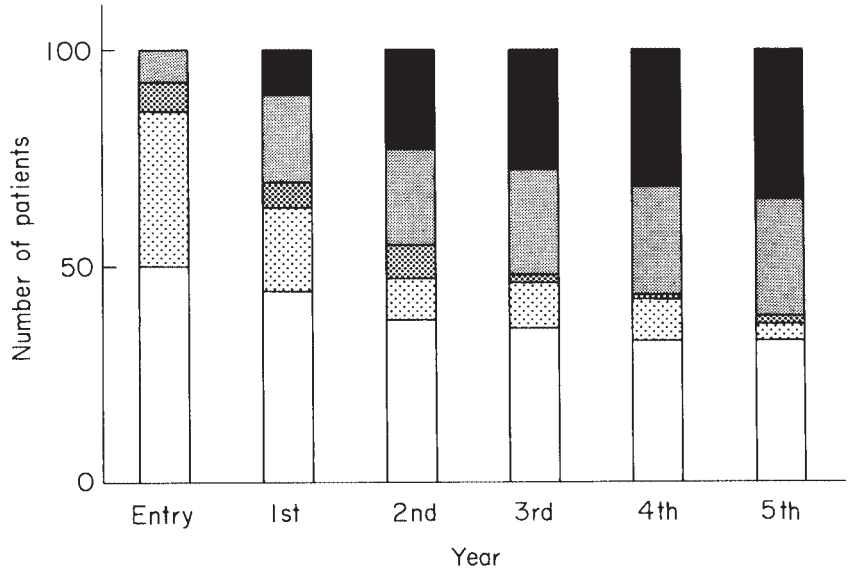

Fig. 4 The results of 5-year-follow-up in JBAR from 1989 to 1994 are illustrated. Thirty-four patients, 49% of the patients who were followed up, were alive without jaundice, while 28 (41%) are dead. Thirty-five patients, 33% of the patients who were entered to the Registry, were lost to follow up.

Alive without jaundice
Alive with jaundice
Unknown
Dead
Lost to follow-up

only with bile drainage and survival, but also with the degree of hepatic fibrosis as emphasized by the Japanese experience. It has been stated that good results are to be expected when the patient is operated on below the age of 60 days. But in this paper the operative results remained almost unchanged until the age of 90 days. The better results in the older age group before 90 days old might be attributed to recent refinement of operative techniques as well as improvement in postoperative management. Apart from short-term results, however, the Tohoku University series of long-term survivors showed better long-term results with below 60 days of age group (Ohi et al. 1990). This is the reason why we advocate the operation should be performed as early as possible.

Ultrasonography was most often utilized as a diagnostic tool for BA, followed by serum lipoprotein X, duodenal aspiration and serum bile acid. Among them duodenal aspiration is felt most recommendable. Because it is an easy, inexpensive, rapid and non invasive test, and its specificity is considerably high as well.

Regarding the operative procedure, original Roux-en Y, Suruga II, and Roux-en Y with intestinal valve were main procedures employed by Japanese pediatric surgeons. There was no difference of survival among the three reconstructions. In terms of the incidence of cholangitis, while the vent surgery and the valve procedure were designed to prevent cholangitis, the original Roux-en Y procedure interestingly yielded the best results. Possible explanations include improved accuracy of diagnosis and exteriorization, which may allow more colonization, in the vented group (Karrer et al. 1990), and excessive peritoneal adhesion in the intestinal valve group. In Tohoku University Hospital, double-valved hepatic portoenterostomy, the long Roux-en Y method with 2 antireflux valves (a spur valve and an intussuscepted intestinal valve), is the standard procedure. It is receiving popularity due to its acceptable results as well as the avoidance of stoma. We believe this procedure is the choice of modification at the time being when it is performed very meticulously.

The selection of choleretic agents is a main concern of postoperative management. Ursodeoxycholic acid, steroid hormones and deoxycholic acid were universally used in Japan. A combination of 2 or 3 drugs was usually administered. But the dosage and length of administration especially in steroids are still controversial. Great care must be taken in the selection of the drugs and the dosage schedule should be modified to achieve maximum therapeutic effectiveness, yet minimize the chance of toxicity. In this regard also, JBAR is expected to play an important role.

Jaundice decreased and disappeared in 37 and 62, respectively, among 177 cases who underwent reoperation in this series. These results seemed unacceptable even in Japan, where brain death has not legally approved yet, and thus liver transplantation is still more difficult modality to employ than in the United States, Australia, or European countries. In the era of liver transplantation, reoperation for BA should be more selevtively indicated. It was reported that

the patient with cessation of good bile drainage after the initial corrective surgery was believed the only indication of reoperation (Ibrahim et al. 1991).

The portoenterostomy and liver transplantation for BA are not competitive procedures but they are now considered by most pediatric surgeons as combined or sequential therapy for this disease (Vacanti et al. 1990; Laurent et al. 1990; Otte et al. 1994).

Judging from the population of Japan and the incidence of this disease, approximately 90% of patients might be registered every year. In this respect, JBAR has been successfully carried out. However, in terms of early diagnosis/operation or operative outcome, unfortunately the results of the Registry were not satisfactory enough. To our regret, 33% of patients were lost to follow-up during the first 5 years. All of our efforts have to be continued to maximize the chance for survival in patients with BA. And we believe the Japanese Biliary Atresia Registry is one of them.

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