TABLE 2. Types of ICH as determined by head CT scans upon admission and/or MRI/MRA during hospitalization, and subsequent procedures performed and outcomes

Case	Sex	Onset of ICH, d	Type of ICH	MRI/MRA during hospitalization (1st–5th wk after admission)	Invasive procedure	Outcome	FU duration, mo
1	F	50	IPH	NA	—	Died	278
2	F	54	IPH, MS(+)	NA	—	Died	36
3	F	66	SDH, IPH, MS(+)	P/O ICH; bilateral SDH; left EDH; bilateral cerebral atrophy; ventricle enlargement; encephalomalacia	Craniotomy	Died	33
4	F	76	SAH	Left temporal lobe encephalomalacia; old SAH	—	Alive (LDLT)	108
5	F	47	SAH, IPH, MS(+)	Laminar necrosis; ventricle enlargement; corpus callosum atrophy; bilateral brain atrophy; encephalomalacia; old SAH; and IPH	—	Alive (LDLT)	80
6	F	69	SDH, MS(+)	P/O ICH; SDH; laminar necrosis; encephalomalacia of left MCA territory	Craniotomy	Alive	75
7	F	72	SDH, MS(+)	Acute bilateral SDH; no new hemorrhage	—	Alive	22

EDH = epidural hematoma; FU = follow-up; ICH = intracranial hemorrhage; IPH = intraparenchymal hemorrhage; LDA = low-density area; LDLT = living donor liver transplantation; MCA = middle cerebral artery; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MS = midline shift; NA = not applicable; P/O = postoperative; SAH = subarachnoid hemorrhage; SDH = subdural hemorrhage.

TABLE 3. Results of routine laboratory examinations, coagulation data, and therapy administered upon admission

	Routine laboratory examination					Coagulation data							
						Before vit K administration						After vit K administration	
Case	Hb, g/dL	Platelets, 10^4 cells/μL	AST, g/dL	ALT, g/dL	DB, mg/dL	HPT, %	INR	PIVKA-II, arbitrary unit/mL	PT, s	APTT, s	Therapy	PT, s	APTT, s
1	8.6	23.3	184	97	6.8	<10			No data	No data	Vit K 0.5 mg/kg IV	11.8	34.9
2	7.3	20.8	238	145	9.2	<5			50.3	198.7	Vit K 1 mg/kg IV + FFP	12.4	36.1
3	4.1	38.7	152	101	4.64		3.36	>40	36.2	67.3	Vit K 1 mg/kg IV + FFP	13.1	32.5
4	4.6	48	224	107	9.82				>200	>200	Vit K 1 mg IV + FFP	18.5	37.7
5	8.5	39	155	124	44.79	70.2	1.31	114	>200	>200	Vit K 1 mg IV + FFP	13	26.4
6	10.5	41.3	138	91	9.6			24.7	>50	>200	Vit K 1 mg IV + FFP	11.7	41.6
7	8.0	61.1	43	38	3.2	119	22.7	>75	No data	>150	Vit K 0.5 mg/kg IV (at other hospital)	13.6	40.3

ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; DB = direct bilirubin; FFP = fresh frozen plasma; Hb = hemoglobin; HPT = hepaplastin; IV = intravenous; INR = international neutralized ratio; PIVKA-II = protein induced in vitamin K-II; PT = prothrombin time.

TABLE 4. Results of follow-up at 2 years of age in BA patients with ICH

Case	Sex	Development assessment	Detail developmental description (maximum ability compared with age)	EEG	Laboratory examination		
					AST, g/dL	ALT, g/dL	DB, mg/dL
1	F	Developmental delay	NA	NA	236	223	9.4
2	F	Developmental delay	NA	NA	255	135	11.2
3	F	Developmental delay	NA	NA	124	59	21.1
4	F	Cognitive impairment	Motor ≈ 2 y 4 mo, social ≈ 2 y 4 mo, speech ≈ 1 y 8 mo	Abnormal/polyspike (subclinical seizure)	151	98	2.9
5	F	Developmental delay	Motor ≈ 1 y 2'mo, social ≈ 1 y 9 mo, speech ≈ 1 y 1 mo	Abnormal EEG (poor activity in left hemisphere)	102	80	0.2
6	F	Normal development	Normal; mild right hemiplegia (upper extremity stronger)	Abnormal EEG (lazy activity in left frontal lobe)	32	19	0.0
7	F	Normal development	Normal	Normal	34	12	0.1

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BA = biliary atresia; DB = direct bilirubin; EEG = electroencephalography; ICH = intracranial hemorrhage; NA = not available.

LDA was found in the left hemisphere. In addition, neurologic sequelae such as right hemiparesis were observed. In contrast, head CT in case 7 also showed SDH and MS at admission; however, during follow-up, head CT showed a complete resolution and no LDA was found. Clinically, case 7 also did not show any neurologic sequelae (Fig. 1).

DISCUSSION

Several recommendations for vitamin K administration had been proposed for all of the newborn infants (12); however, the prophylactic administration of vitamin K is not sufficient to prevent bleeding disorders in infants with BA (4,6). As described in our study, all of our cases received 2 mg prophylactic oral administration of vitamin K during the neonatal period; nevertheless, ICH still occurred in 7.95% of our patients with BA. The prophylactic failure is probably the result of their increased bleeding tendency caused by secondary late-type VKD associated with cholestasis-induced malabsorption of vitamin K in the digestive tract, as mentioned in previous studies (2,6). This is supported also by a study by Van Hasselt et al (13), which described the risk of VKDB in breast-fed infants with BA receiving 25 μg oral vitamin K from

TABLE 5. Results of follow-up head CT scan and persistent neurologic sequelae

Case	Sex	Type of ICH at admission	CT scan (last examination)	Neurologic sequelae
1	F	IPH	LDA consistent with encephalomalacia, cerebral atrophy, ventricle enlargement	Mental retardation
2	F	IPH, MS(+)	NA	Epilepsy
3	F	SDH, IPH, MS(+)	Cerebral atrophy (bilateral), LDA consistent with encephalomalacia, ventricle enlargement	Developmental delay
4	F	SAH	LDA consistent with encephalomalacia	No sequelae
5	F	SAH, IPH, MS(+)	LDA consistent with encephalomalacia, ventricle enlargement	Mild mental retardation; mild hemiparesis
6	F	SDH, MS(+)	LDA consistent with encephalomalacia, slightly enlargement of lateral ventricle	Mild hemiparesis
7	F	SDH, MS(+)	No abnormalities (LDA [−])	No sequelae

CT = computed tomography; IPH = intraparenchymal hemorrhage; LDA = low-density area; MS = midline shift; NA = not available; SAH = subarachnoid hemorrhage; SDH = subdural hemorrhage.

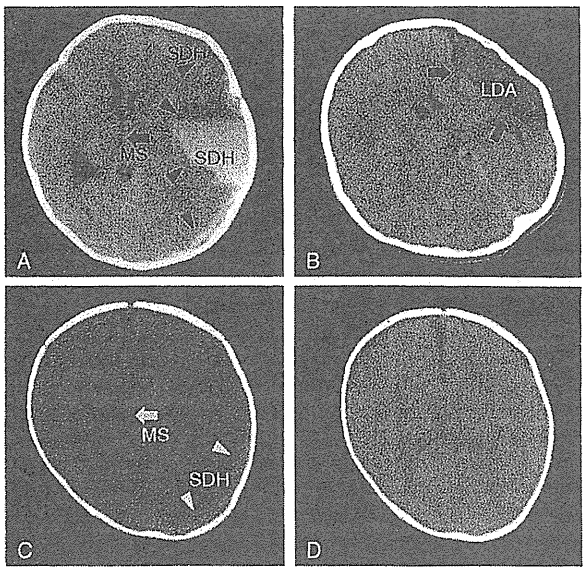

FIGURE 1. Comparison of head computed tomography (CT) scans at admission and during follow-up. A, Head CT of case 6 at admission, showing subdural hemorrhage (SDH) (arrowhead) and midline shift (MS) (arrow). B, Head CT of case 6 during follow-up, showing low-density area (LDA) consistent with encephalomalacia in the left hemisphere without new hemorrhage (arrow). C, Head CT of case 7 at admission, showing SDH (arrowhead) and MS (arrow). D, Head CT of case 7 during follow-up, showing no abnormalities.

the second week until the end of the 13th week was 8 to 10 times higher than in breast-fed infants receiving either a higher weekly oral prophylaxis dose or intramuscular (IM) prophylaxis at birth. More than 80% of the infants in that study developed VKDB by the time that cholestasis was diagnosed, and 43% presented with an ICH. A comparison study of VKD and VKDB risk in cholestatic jaundice infants who received regular infant formula and hypoallergenic formula by Van Hasselt et al (14) also reported that an increased risk is predominant in cholestasis infants receiving (whey-based) hydrolyzed formula. In the present study, we also describe that of 7 patients, 4 patients received BF only, whereas 1 patient received only regular FM and 1 patient received both BF and FM; however, in the present study we could not overestimate that BF is related to the development of ICH because of a lack of data about infant nutrition from the rest of the patients with BA who did not have ICH complication. Moreover, regarding the administration route of vitamin K, Komatsu et al also described a case of ICH in 2 infants with the late type of VKD despite 3 administrations of 2 mg oral vitamin K after birth, at 5 days old and 1 month old (15). Although the underlying diseases of these patients until hospital discharge remain undetermined, it is suggested that prophylactic oral vitamin K failed to prevent ICH in late-type VKD.

In the present study, all of the patients fulfilled the criteria of VKDB. Elevation of the PT at admission (range 36.2 to >200 seconds) was found in all of the patients with available data and was rapidly improved after administration of IV vitamin K and FFP (range 11.7–18.5 seconds). One patient (case 1) did not have exact PT data upon admission (referral information from the previous hospital was not complete); only PT and APTT were written as elevated and the patient had been administered with 2 mg vitamin K intravenously; however, hepaplastin test upon admission was <10% and PT after 24 hours' administration of vitamin K returned to the normal level, combined with improvement of bleeding tendency. Therefore, we concluded that case 1 fulfilled the VKDB criteria, and counted as ICH-associated VKDB. In addition, an elevated PIVKA-II level was also found in all 3 patients whose PIVKA-II levels were measured and 1 patient just written elevation of PIVKA-II in the referral letter. Grossly abnormal PT with a rapid normalization of coagulation test and bleeding tendency after vitamin K administration combined with an elevation of PIVKA-II level, despite a normal platelet count, were characteristic findings of laboratory examinations in patients with VKD (7,10,16,17). The severity of the coagulation disorder was not inversely proportional to the value of hemoglobin. Nevertheless, the severity of anemia was probably related to the symptoms at admission, as shown in our 2 patients with severe anemia, both of whom had dyspnea as a presenting symptom. Nevertheless, dyspnea could also occur as a cause of brain swelling or compression.

In the present study, intraparenchymal hemorrhage with MS was the most common lesion found in CT images. These findings are different from other reports, which found SDH and subarachnoid hemorrhage as the most common types of ICH (8,16). In addition, in 2 of 7 of our cases, >1 lesion was found on CT. This finding is similar to Majeed et al (8), who reported that most of the children presenting with VDKB had hemorrhage in multiple sites, and pallor was seen in all of the infants (100%). Recently, magnetic resonance (MR) imaging was widely used in clinical practice for neonates with brain injury because of its high sensitivity for depicting a developing brain. MR can provide greatly detailed images of brain structures without exposing infants to ionizing radiation (18). CT is frequently used in workup in children with sudden onset of neurologic symptoms, especially to rule out acute hemorrhage. In addition, MR demands particular care with regard to patient transport, monitoring of vital signs, and optimization of acquisition techniques (use of appropriate coils, sequences, and protocols) (18–20). In our institution, we use head CT as a diagnostic tool for emergency brain injury, especially because CT was faster as compared with MR (<5 minutes), did not require any sedation, and allows close monitoring of vital signs during evaluation of unstable neonates after ICH. During hospitalization, except for 2 patients who were born before 1995, MR imaging and MR angiography were done after patients' conditions were stabilized, to obtain an accurate evaluation, which revealed a more clear description of late brain complications as early as the first week after ICH (Table 2).

In spite of the wide variety of lesions in our cases, craniotomy was done only in 2 cases, without correlation to the lesion(s) itself, and was done before laparatomy. The indications of craniotomy of our patients were increased intracranial pressure with worsening of consciousness and the presence of anisocoria suggesting severe brain compression caused by large hemorrhage. The other cases were treated supportively or were treated for increased intracranial pressure or cerebral edema, if suspected. With or without surgical intervention for hematomas, a laparatomy was performed in all of our patients on an average of 22.3 days after the onset of evacuation of ICH and 9 days at the earliest. This was based on the fact that the Kasai portoenterostomy has become the primary surgical treatment for uncorrectable BA (21–23). In patients with BA with ICH as a presenting symptom, early Kasai portoenterostomy is also recommended. In the patients presenting with ICH and in those who have undergone craniotomy, early Kasai portoenterostomy is possible only when both hemorrhage and the bleeding tendency are well controlled. IV administration of vitamin K at 0.5 to 1.0 mg/kg, with or without addition of FFP given concurrently for more rapid restoration, is effective in patients with VKDB (16,24). Vitamin K administration had been reported to improve bleeding tendency within 1 hour and normalizes the

agulation within several hours, to facilitate even an urgent aniotomy (6). In our patients with or without craniotomy, no fficulties in hemostasis or recurrent hemorrhage were noted after itial administration of vitamin K IV and FFP. These findings iggest that surgical intervention for ICH has no adverse effects on e subsequent surgical management of BA if coagulation disorders e managed properly.

Studies on the long-term follow-up reported that some eurologic sequelae, such as developmental delays, mental tardation, and epilepsy, were observed in more than half of the atients with ICH caused by VKD (25,26). In the present study, evelopmental delay in all of the evaluation aspects showed in patients at 2 years of age, which in 3 patients remains until the end f study follow-up. At further follow-up until the end of the present udy (at 22–278 months), none of the patients died of ICH. Causes f death of our patients were end-stage liver diseases in those unable o undergo liver transplantation, in which the progressivity of the isease already could be seen at 2-year follow-up (Table 4). Follow-p imaging studies obtained using head CT scans showed an LDA onsistent with encephalomalacia in the left hemisphere in 5 cases. Until the end of our observation, some neurologic sequelae ersisted in 5 of 7 cases. The type of neurologic sequelae found /ere mental retardation in 2 cases, epilepsy in 1 case, hemiparesis 1 2 cases, and developmental disorder in 1 case, with no correlation o the substantial ischemic brain damage demonstrated on CT. Mental retardation in case 1 was determined by an IQ measurement f 47 combined with a marked decreased ability to interact with ndividuals at 20 years of age without mental retardation. These indings are in agreement with the latest head CT evaluation, which howed a marked cerebral atrophy, cerebral ventricle enlargement, nd encephalomalacia. Unfortunately, the MRI/MRA evaluation is ot available in this patient; however in case 5, mental retardation vas determined by an IQ measurement of 70 at 6 years of age, ombined with a decreased ability to speak, write, and understand onversation. In this patient, in addition to the MRI/MRA findings t 3 months of age (Table 2), a follow-up head CT showed brain trophy, ventricle enlargement, and encephalomalacia. Furthermore, MRI evaluation also showed atrophy at the splenium and he posterior part of the corpus callosum, which explains the low IQ neasurement (figure not shown). In spite of mental retardation, case 5 was enrolled in mainstream elementary school because the mental retardation was on the borderline. Compared with Akiyama et al (3), who found only 2 of 15 patients with long-term neurologic sequelae, the present study showed a higher incidence; however, the long-term outcomes observed in our cases were similar to those for other cases of ICH, which were not associated with BA. In addition, the neurologic sequelae found in our patients did not correlate with the severity of the clinical findings, the laboratory findings, or the need for craniotomy. These findings suggest that the long-term outcomes cannot be predicted from examinations during admission, and even a mild lesion should be managed properly.

In conclusion, although vitamin K prophylaxis had been given during the neonatal period, VKDB-associated ICH was still found in 7.95% of patients with BA, of whom 4 received exclusive BF. In regard to the low concentration of vitamin K in breast milk compared with regular FM, apparently healthy infants who received exclusive BF during 6 months of life and oral prophylactic vitamin K should be monitored closely. Based on our long-term observation, even though the rate of ICH in patients with BA is low, it should be managed properly to prevent long-term neurologic disability, as shown in 5 of our patients. Based on our study and other studies from Japan, we suggested that 2 mg of oral vitamin K 3 times during the neonatal period should be reevaluated for their protective dose against ICH. A study comparing routes of administration of neonatal vitamin K should be conducted to investigate the effectiveness of oral and IM administration of vitamin K in preventing the occurrence of ICH in infants with BA.

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ORIGINAL ARTICLE

A morphological study of the removed livers from patients receiving living donor liver transplantation for adult biliary atresia

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Abstract
Background In liver transplantation (LT) for adult biliary atresia (BA), we often encounter a cirrhotic deformation of the native liver. We aimed to investigate a morphological study of the removed livers and the patient's clinical status.
Methods We examined 8 BA patients who had undergone LT in adulthood at our hospital. The presence of hypertrophic or atrophic areas of the removed liver was recorded macroscopically. We graded the microscopic findings in the porta hepatis area, a hypertrophic area, and an atrophic area, respectively. Moreover, we investigated the relationship between these morphological findings and the pre-transplant clinical status (MELD score).
Results Macroscopically, a hypertrophic area existed in central liver in all cases (8/8 cases), while an atrophic area was existed in peripheral liver (7/8 cases). Microscopically, an atrophic area was the most severely impaired, while the porta hepatis and hypertrophic area were relatively intact. The pathological score in a compensatory hypertrophic area was strongly correlated with the MELD score.
Conclusions This study suggests that the partial shrinking is not uncommon in BA cirrhotic liver. It may be due to the imbalance of bile drainage by the different segment. The patient's pre-transplant status depends on the compensatory hypertrophic liver.

Keywords Biliary atresia · Removed liver · Hypertrophy · Atrophy · MELD score

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Introduction

The prognosis of patients with biliary atresia (BA) has improved since the introduction of hepatic portoenterostomy by Kasai and his colleagues in 1959 [1]. Although the majority of patients have decreased or a complete lack of jaundice, and have a normalized liver function test transiently after Kasai's portoenterostomy (KP) [2], most patients unfortunately experience the progression of liver dysfunction related to ongoing liver fibrosis and postoperative complications such as cholangitis, portal hypertension, esophageal varices, and hepatic failure.

Liver transplantation (LT) is the only curative treatment for cirrhotic BA, although some patients are now reaching adulthood with their native liver after treatment with KP. However, most BA patients still have to eventually undergo LT. In LT for adult BA, we often encounter a cirrhotic deformed native liver. The pathogenesis of the deformity of the cirrhotic BA liver is still unclear. In this paper, we aimed to investigate the importance of a long-term biliary drainage by a morphological and clinicopathologic study of the livers removed during living donor liver transplantation for adult BA. Moreover, we also investigated the relationship between the patients' pre-transplant status and the histopathology of the removed livers.

Patients and methods

We examined 8 BA patients who had undergone living donor LT in adulthood (19–28 years old) at Department of Pediatric Surgery in Kyushu University Hospital between October 1996 and December 2009. All removed whole livers at LT were examined. The livers were macroscopically examined for the presence of hypertrophic or atrophic areas. Standard histology blocks were taken from the porta hepatis area, the hypertrophic area, and the atrophic area (about 10 blocks per case). Specimens were stained with hematoxylin and eosin, and the extent and distribution of fibrosis was assessed. The grade of liver damage based on the findings, including intrahepatic inflammation, fibrosis, ductular reaction, and bile congestion, was assessed and scored in a porta hepatis area, a hypertrophic area, and an atrophic area, respectively.

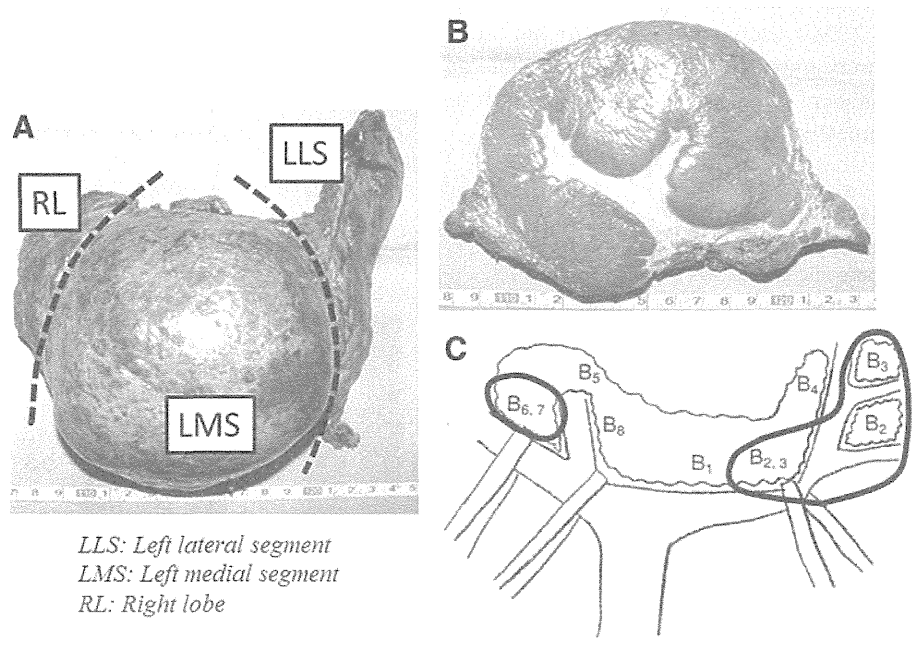
The histological scoring was determined as follows: (1) intrahepatic inflammatory cells proliferation [none: A0/score 0, mild: A1/+1, moderate: A2/+2, and severe: A3/+3], (2) fibrosis [none: F0/0, fibrous dilatation of periportal area: F1/+1, bridging fibrosis: F2/+2, fibrosis with deformed centrilobular construction: F3/+3, and cirrhosis: F4/+4], (3) ductular reaction [none: D0/0, mild: surrounding less than 1/3 of the portal area (D1/+1), moderate: surrounding 1/3–2/3 of the portal area (D2/+2), and severe: surrounding more than 2/3 of the portal area (D3/+3)], (4) bile congestion [none: B0/0, mild (in hepatocytes): B1/+1, moderate (in the ductular area): B2/+2, and severe (in the bile duct at the centrilobular area): B3/+3.] This pathological grading as for A and F is a standard classification described in the previous report [3], while the grading system as for D and B is our original classification. These histological features thought to be important in the evaluation of a cholestatic liver damage were selected according to the previous report [4]. These scoring were reviewed blindly by two pathologists.

Moreover, we investigated the relationship between these morphological findings and the patient's pre-transplant clinical status (model for end-stage liver disease, MELD score) which is calculated by serum creatinine, bilirubin and international normalized ratio (INR) of prothrombin time as described in the previous literature [5]. In this study, the MELD score was calculated in all cases by the blood test performed just before LT. This study was performed according to the Ethical Guidelines for Clinical Research published by the Ministry of Health, Labor, and Welfare of Japan on July 30, 2003.

Results

Macroscopic findings in the removed livers

Macroscopically, all removed livers were able to be clearly divided into atrophic and compensatory hypertrophic areas as shown in Fig. 1. The macroscopic findings in all cases are summarized in Table 1. The atrophic areas exist in the right anterior segment (RAS) + right posterior segment (RPS) + left lateral segment (LLS) in three cases, only LLS in three cases, RAS + RPS in one case, and LLS + left medial segment (LMS) in one case. On the



LLS: Left lateral segment
LMS: Left medial segment
RL: Right lobe

Fig. 1 **a** A deformed liver removed at liver transplantation in adulthood. The liver shows markedly atrophic in the right lobe and left lateral segment, and remarkable hypertrophy in left medial segment. **b** A divided surface shows the two distinct areas. **c** The micro bile duct orifice from each area at the hilum. The orifice from the atrophic peripheral liver locates the bilateral sides at the hilum

Table 1

Case	Age at LT (year)	Sex	Atrophic area	Hypertrophic area
1	19	F	LLS, RAS, RPS	LMS
2	23	F	LLS, RAS, RPS	LMS
3	25	M	LLS, LMS	RAS, RPS
4	24	F	LLS	RAS, RPS
5	23	M	LLS	RAS
6	28	F	LLS	LMS
7	27	F	RAS, RPS	LLS, LMS
8	28	F	LLS, RAS, RPS	LMS

LLS left lateral segment, *LMS* left medical segment, *RAS* right anterior segment, *RPS* right posterior segment

other hand, the hypertrophic areas were present in LMS in four cases, RAS + RPS in two cases, RAS in one case, and LLS + LMS in one case. The atrophic area was generally located in peripheral liver like LLS (7/8 cases). The hypertrophic area was found in central liver such as LMS and RAS in all cases (8/8 cases).

Microscopic findings in the removed livers

Microscopically, the cirrhotic changes in the peripheral liver with various sizes of nodules separated by fibrous bands with a mild chronic inflammatory infiltrate in the stroma, and marked loss of the interlobular bile duct and slight cholestatic changes were also seen. On the other hand, the histology of the hypertrophic central liver indicates the diffuse regenerative hyperplasia of hepatocytes and a relatively normal appearance. The mean score in each area with regard to the four parameters is shown in Fig. 2. Microscopically, the atrophic areas were the most severely impaired, and the hypertrophic and porta hepatis areas were relatively normal grade with regard to all four parameters.

The relationship between the microscopic findings in the removed livers and the patients' pre-transplant status (MELD score)

The microscopic pathological scores in the hypertrophic area and MELD score in all cases are summarized in Fig. 3a. A significant positive correlation between the sum of the four pathological scores in the compensatory hypertrophic area and MELD scores was found (Fig. 3b).

Discussion

More than 50 years have passed since Kasai and his colleagues [1] introduced hepatic portoenterostomy as an option for biliary drainage in patients with non-correctable types of BA. Although KP has been accepted worldwide as the primary operation for treating non-correctable BA, long-term follow-up data have shown evidence of progressive liver disease in a high percentage of patients [6]. For example, Shinkai et al. [6] reported that at least half of the adult survivors who had received KP would require LT in the future because they already had liver cirrhosis at age 20. Therefore, some researchers do not consider KP to be a curative treatment by itself, but rather a bridge to LT [7].

In LT for adults with BA, we often encounter a cirrhotic deformed liver. In the present study, all removed livers were morphologically divided into two distinct areas: the atrophic area was located in the peripheral liver like LLS (7/8 cases) and the hypertrophic area was in the central liver such as LMS and RAS in all cases (8/8 cases). This result is supported by the previous published data [8–10]. Yeung et al. [8] reported that the hepatectomy specimens showed a central zone of relatively normal parenchyma and a peripheral zone of cirrhosis. Takahashi et al. [9] reviewed five livers from patients undergoing OLT for BA. All explants showed a hypertrophic perihilar region in segment 4 with near normal bile ducts and atrophic, fibrotic areas

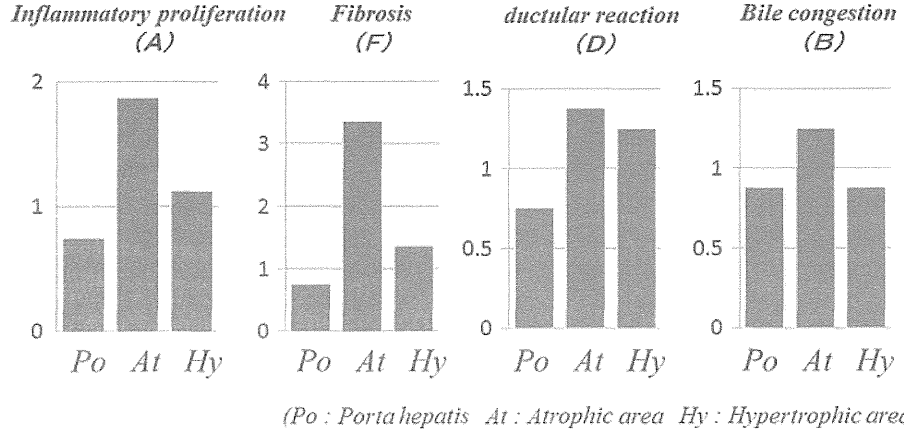


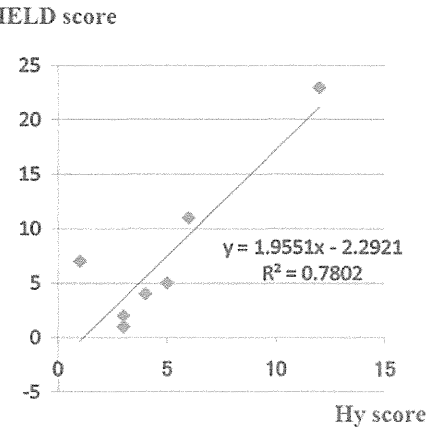
Fig. 2 The mean pathological scores of the removed livers. The atrophic area shows the highest score in all parameters [inflammatory cells proliferation (*A*), fibrosis (*F*), ductular reaction (*D*), bile congestion (*B*)], followed by hypertrophic area and porta hepatis. In hypertrophic and porta hepatis areas, the score demonstrated nearly normal compared to the atrophic area

Fig. 3 The relationship between the histological scores and the MELD scores. **a** The sum of pathological scores (*A, F, D, B*) in the compensatory hypertrophic area and MELD score in each patients. **b** There is a strong correlation between the pathological scores in the compensatory hypertrophic area and MELD score

A

case	Hy score	MELD score
1	3	1
2	3	2
3	5	5
4	3	1
5	4	4
6	1	7
7	12	23
8	6	11

B



(Hy : Hypertrophic area)

with ductopenia more peripherally. Ijiri et al. [11] reviewed post-Kasai hepatectomy specimens; a large central regenerative nodule with relatively normal liver architecture was found in three older children and a poorly defined central hypertrophic area in another two cases. Taken all together including our study, the long-term BA cirrhotic liver has two distinct areas in most cases. This partial shrinking pattern is different from the cirrhosis caused by the other etiology, which is mostly totally shrunken. This different shrinking pattern would come from the imbalance of bile drainage by the different areas.

In the present microscopic study, the pathological scores were worse in the atrophic area than in the hypertrophic and the porta hepatis areas. Interestingly, the bile congestion is not always diffusely occurred, the atrophic area showed the most severe. In other words, there is an imbalance of bile drainage. From this finding, the following two explanations would be discussed. The first is the inherent regional differences in the central versus peripheral BA liver and the second is the differences of bile drainage after KP from two areas. Ductopenia is well documented in liver biopsies from patients with BA after KP. Kasai et al. showed that intrahepatic ductopenia was progressive with increasing age, it is the character of BA liver and may progress inherently earlier in the peripheral liver. Regarding the bile drainage after KP, many pediatric surgeons have historically paid a lot of attentions to the technical aspects of KP procedure.

The extent of dissection at KP may be important for the biliary drainage. However, the optimal depth and extent of fibrous tissue transection and the site of suturing placement are still controversial. Many pediatric surgeons tried modifying the original KP, whose fibrous tissue dissection and anastomosis area were actually quite shallow and limited, to improve results, the anastomosis had been extended laterally in order to drain from the lateral micro bile ducts [12, 13]. However, recently, the extended lateral wide dissection has been thought to cause more injury to micro bile ducts and could in fact only worsen the risk for injury. Superina et al. [14] reported that the extent of hilar dissection had no effect on the KP outcome. Moreover, the recently reported outcome of laparoscopic KP with narrow hilar dissection shows good jaundice clearance [15]. Although we are not able to conclude the optimal extent of transection from only our results, the long-term bile drainage especially from the peripheral liver was thought to be a critical problem at KP.

In the cirrhotic liver, the hypertrophic segment must be a functional area, because this area had nearly normal histology. It is interesting to note that the pathological scores in the compensatory hypertrophic area demonstrated a significant correlation with the MELD scores in the present study. MELD score is generally used as a prognostic indicator for patients with advanced chronic liver disease waiting for LT on the United Network for Organ Sharing (UNOS) waiting list [5]. To our knowledge, this is the first report that demonstrated the significant correlation between the pathological findings in the compensatory hypertrophic area of the cirrhotic liver and the MELD score. The removed BA livers in infancy or early childhood are not always divided into two distinct areas such as the present adult cases and look diffusely shrunken. In other words, only the "successful" adult KP cases could have the compensatory area and show the lower MELD score.

In conclusion, the livers removed at LT for adult BA generally showed the atrophic area to be localized in peripheral liver. It has clinical implications that the morphological cirrhotic pattern after KP was similar in all the present cases. Although we are not able to conclude the optimal extent of transection from only our results, the long-term bile drainage especially from the peripheral liver might be a key factor. In addition, from our result of

MELD analysis, we could conclude that the histological status of the compensatory hypertrophic area in "successful" adult BA liver was a predictive factor of the necessity of liver transplantation.

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4．母子健康手帳に便色見本が掲載された意義

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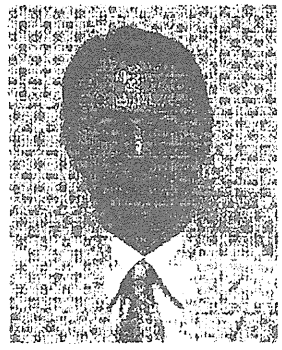
KEY WORDS
胆道閉鎖症
スクリーニング
便色カード
ビタミンK欠乏性出血症
葛西手術


Akira Matsui

はじめに

胆道閉鎖症は，新生児および乳児の肝外胆管が，原因不明の炎症のために閉塞する，破壊される，あるいは消失するために，肝から腸へ胆汁を排出できない疾患である（**図1**）。出生児約10,000人に1人が罹患する稀な疾患だが，同年齢の肝・胆道系疾患の中では死亡率が最も高い。予後不良の理由の一つとして発見の遅れがあげられ，早期発見のためのスクリーニングの必要性が強調されてきた。私どもはその方法として患者および生後1カ月の健常乳児の便を写真撮影してカラースケールとした便色カードを考案し，これを9つの自治体で使用してきた。厚生労働省は平成24年度からこの便色カードを，母子保健法施行規則の一部を改正する省令（平成23年12月28

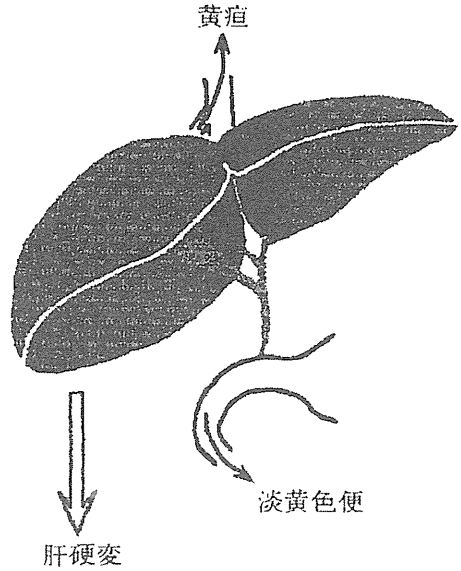


図1　胆道閉鎖症の病態
胆管が閉塞している．

〒157-8535　東京都世田谷区大蔵2-10-1

日厚生労働省令第158号）により，わが国で配布されるすべての母子健康手帳に掲載することを全自治体に義務付けた。本稿では母子健康手帳に掲載される便色カードの意義，使用法について概説する。なお医療機関，各市区町村関係の方は，詳細に関して国立成育医療研究センターのホームページ[1]を参照されたい。

Ⅰ．胆道閉鎖症の症候

胆道閉鎖症の３主徴は遷延性黄疸，淡黄色便，濃黄色尿である。

新生児の90％に見られる生理的黄疸は生後14日までに肉眼上消失する。これに対して生後14日を超えても認められる黄疸を遷延性黄疸という。この遷延性黄疸の大部分は，母乳性黄疸である。母乳栄養児の約15％は遷延性黄疸を呈する。母乳性黄疸は黄色調が明るく，生後２，３カ月までに自然軽快し，無害である。その診断は血清直接型ビリルビン値が総ビリルビン値の20％以下で，ほかの診断が除外でき，かつ消失して初めて確定する。

胆道閉鎖症の黄疸も遷延性黄疸を呈する。その黄疸は消失せずに持続する，あるいはいったん消失した黄疸が再び現れてくる。非水溶性のビリルビンは肝細胞でグルクロン抱合されて水溶性になるが，胆管が閉鎖しているため胆道系に排泄されずに，肝細胞から末梢血中に逆流し，脂肪組織に沈着して皮膚や眼球結膜を黄染する。生後１カ月ごろの胆道閉鎖症の患児の黄疸はそれほど強くないことが多く，色調もくすんだ黄色なので見逃されやすい。

淡黄色便はもっとも特異的な症状のひとつである。淡黄色便とは黄色みがうすい色の便という意味だが，生後１カ月ごろの胆道閉鎖症患児の便色は，しいて言うならうすいベージュ色に近い。胆道閉鎖症患児の70～80％は生後４週までに便の黄色調がうすくなって淡黄色になり，残りの20～30％も多くは生後２カ月までに淡黄色便を発症する。

濃黄色尿は胆汁色素であるビリルビンが尿中に出ることによるもので，生直後からしばしば認められる症状である。黄疸が著明な時には尿が暗褐色になる。オムツに尿だけがしみている時には注意して見るとよい。これに対して母乳性黄疸で増加するのは非抱合型ビリルビンで尿中には出ないため，尿が強く黄染することはない。

胆道閉鎖症では，頭蓋内や消化管，臍などにビタミンＫ欠乏による出血を起こすことがある。ビタミンＫは胆汁中の胆汁酸によりミセルとなって腸で吸収される。しかし胆道閉鎖症では胆汁が腸に排泄されないため，ビタミンＫの吸収が不良になる。ビタミンＫは血液の凝固を助けるので，これが不足すると出血を起こす。頭蓋内出血では突然の哺乳力低下，意識レベルの低下等の重い神経症状を認めることがある。胆道閉鎖症では肝脾腫を認めることが多いが，それ以外には生後１カ月ごろの本症患児は一般に全身状態良好である。

Ⅱ．淡黄色便の臨床的意義

淡黄色便を認める疾患は胆道閉鎖症だけではない。先天性胆道拡張症のように胆管が狭窄する外科的疾患でも認められ，放置すると肝硬変を来すので早期手術が必要である。内科的疾患でも敗血症や尿路感染症，梅毒は，抗菌剤投与により胆汁うっ滞が軽快するので早期に除外すべきである。その他の内科的疾患は肝内胆汁うっ滞を来すものとして，鑑別診断の対象になる（表）。

またこれらすべての疾患において，胆汁酸排泄が減少する結果，ビタミンＫ欠乏性出血症の危険がある。この場合，半減期の短いビタミンK_2の経口投与では効果が不十分である。淡黄色便を認める児は，ただちに入院・

表　新生児・乳幼児胆汁うっ滞の分類（Mowat を改編）

非閉塞性胆汁うっ滞		
	新生児肝炎（特発性）	
	二次性肝内胆汁うっ滞	
		感染性（新生児肝炎症候群）
		ウイルス：サイトメガロウイルス，B型肝炎ウイルス，風疹ウイルス，単純ヘルペスウイルス，水痘・帯状疱疹ウイルス，コクサッキーウイルス，エコーウイルス，ヒトパピローマウイルスなど
		細菌：大腸菌（尿路感染症，敗血症），梅毒，結核，リステリアなど
		原虫：トキソプラズマ
		遺伝性・奇形症候群：Alagille 症候群
		α1-アンチトリプシン欠損症
		（膵）嚢胞性線維症
		進行性家族性肝内胆汁うっ滞（良性反復性肝内胆汁うっ滞を含む）
		シトリン欠損による新生児肝内胆汁うっ滞
		Aagenaes 症候群
		Donahue 症候群
		代謝異常
		アミノ酸：高チロシン血性
		脂質：Wolman 病
		Niemann-Pick 病3型
		Gaucher 病
		acyl-CoA 脱水素酵素欠損症
		炭水化物：ガラクトース血症
		フルクトース血症
		糖原病　Ⅲ/Ⅳ
		phosphoenolpyruvate carboxykinase deficiency
		胆汁酸：トリヒドロキシコプロスタン酸血症
		Δ4-3-Oxysteroid -5β-reductase deficiency
		3β-Hydroxy -Δ5-ステロイド脱水素酵素イソメラーゼ欠損症
		Zellweger 症候群（他のペルオキシゾーム異常を含む）
		金属：新生児鉄貯蔵症
		銅過剰症
		解剖学的異常：先天性肝線維症／乳児多発性嚢胞性腎疾患
		Caroli 病
		非症候性肝内胆管減少症
		ミクロフィラメント機能障害
		染色体異常：21トリソミー
		18トリソミー
		中毒性：完全静脈栄養
		内分泌学的異常：下垂体機能低下症（Septo-optic dysplasia を含む）
		尿崩症
		甲状腺機能低下症
		副甲状腺機能低下症
		副腎機能低下症
		血液学的異常：血球貪食症候群
		そ血症：新生児肝壊死
		自己免疫性：原発性硬化症胆管炎
		自己免疫性肝炎
閉塞性胆汁うっ滞		
	肝外・肝内胆管閉塞：胆道閉鎖症	
	肝外胆管閉塞：先天性胆道拡張症（特発性胆管穿孔を含む）	
	胆石	
	悪性腫瘍	

精査・治療の必要がある。ビタミンK欠乏性出血症も胆道閉鎖症およびそれ以外の胆汁うっ滞性疾患をスクリーニングにより検出すべき根拠の一つである。

Ⅲ. 胆道閉鎖症の診断・治療

血液では血清総ビリルビン値の上昇，直接型ビリルビン値の上昇（1.5 mg/dL 以上），直接型対総ビリルビン比（D/T比）20%以上，AST および ALT 値の上昇，リポプロテイン-X陽性等，臨床検査値の異常を認める。さらに腹部超音波検査，十二指腸液検査などを実施する。これらの結果から胆道閉鎖症を否定できない場合に，開腹手術を行い，肉眼所見および，胆嚢に内腔がある場合には手術的胆道造影によって診断を確定する。

診断確定に引き続いて，肝門部空腸吻合術（以降，葛西手術と略す）を行う。これは東北大学小児外科の葛西が1959年に考案した手術で，現在は Kasai procedure と呼ばれて，世界中の先進国で実施されている。胆道閉鎖症において閉塞した索状胆管組織を一塊として切除し，肝門部に小腸を Roux-Y 吻合する（**図2 a，b**）。この手術の第一の目標は黄疸を消失させること，第二の目標は黄疸が消失したら，自分の肝臓で長期生存することにある。

Ⅳ. 胆道閉鎖症の予後

葛西手術1年後の転帰は，黄疸なく生存が約57%，黄疸有生存が約11%，移植生存が約25%，死亡が約4%である[2]。黄疸の持続する患児はやがて胆汁性肝硬変，慢性肝不全となって，肝臓移植をしなければ死亡する。葛西手術によって黄疸が消失する患児には上行性胆管炎や，食道・胃静脈瘤破裂等による消化管出血を繰り返す場合と，そうした合併症の少ない場合がある。後者の場合には健常児と変わらない生活の質を得て，20歳以上に達する患者もいる。

葛西手術後，自分の肝臓で生存する確率を自己肝生存率という。Nio ら[3]によれば20年自己肝生存率は手術時日齢と負の相関があり，生後60日内であれば43%，61～90日では33%，91～120日では25%，121～150日では7%，151日以降では0になる。にもかかわらず生後60日以内に手術を受ける患児は，今日でも全体の約40%にすぎない。大部分の患児が生後60日以内に葛西手術を受けることができれば，自己肝生存率が上昇するであろう。しかし20年生存した場合にも，その患者には肝硬変があって，いずれ肝移植を必要と

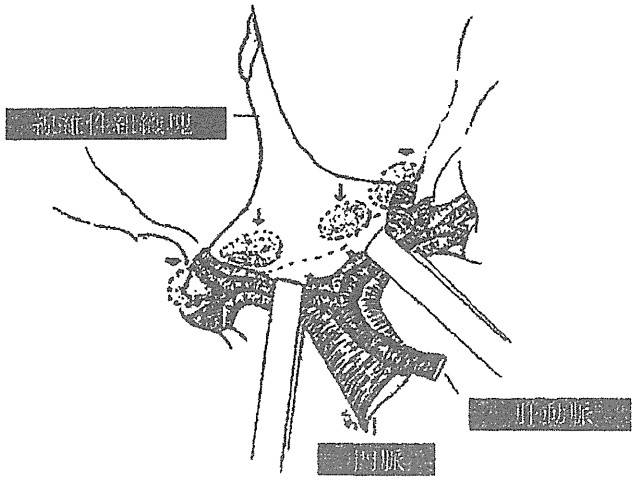


図2 a　葛西手術（線維性組織塊を破線に沿って切除）

図2 b　葛西手術（肝門部空腸吻合術）

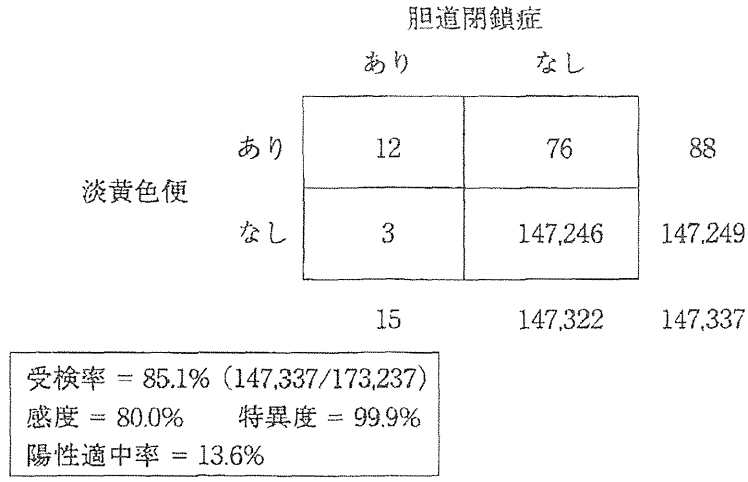


図3　精度の評価（栃木県，Aug. '94 ～ Jul. '03）[8]

することは否定できない[4]。しかしSerinetら[5]は，葛西手術を生後45日以内と46日以降に行った場合では，15年自己肝生存率に12.1%の有意差があることを明らかにした。そして，このことは小児期に肝移植をする必要性を減らすという理由で，胆道閉鎖症のスクリーニングを採用すべきという理論的根拠を与えるとした。

Ⅴ．胆道閉鎖症のスクリーニング法

胆道閉鎖症のスクリーニング法としてこれまでに提唱された方法を大別すると，選択的スクリーニングと非選択的スクリーニングがある。前者は，生後3週で黄疸のある児から毛細管採血をして，血清直接型ビリルビンを測定する方法で，英国の一部で実施されている[6]が，その効果についての報告はない。1994年，私どもが開発して実施した便色カード法[7]は，生後1カ月乳児の便色を，同時期の乳児の便を写真撮影し，カラー印刷して作成した便色スケールの7種類の便色と比べて，その便色番号を保護者に答えさせるものである。

栃木県における9年間のスクリーニング施行の結果，受検率は85%，感度は80%，陽性適中率は13.6%であった（**図3**）[8]。スクリーニングを県レベルで導入した栃木県とそれ以外の地域（日本胆道閉鎖症研究会の全国集計による）とを比較すると，前者において葛西手術時の平均日齢が小さく（54.8±19.9 vs 66.1±29.7），生後60日以内の手術を受けた患児の比率が高い（75.0% vs 48.8%）と推定された（統計学的有意差未検定）。またこのスクリーニングの費用―効用比は34万円/QALY（Quality Adjusted Life Year「生活の質を調整した生存年」）で，1人の患者の1QALYを延長するためにこの検査にかかる費用が34万円であった。ちなみにカナダの研究者の提案では，この値が200万円以下であればこの検査を利用するための強い根拠になる[9]という。その後，初版便色カードによる胆道閉鎖症のスクリーニングは茨城県，札幌市，岩手県，岐阜県，石川県，秋田県，北海道，新潟県，富山市の計9自治体で採用された。

Ⅵ．初版便色カードの長所と短所

初版便色カード法の長所は以下のとおりである。すなわち，①大多数の乳児が受診する1カ月健診の機会を利用できること，②便色に番号を付けて色彩名称による表現の個人差を排除し，母親が淡黄色便の異常性を知らなくても医師に異常を伝えられること，③児の便色調を日常的に観察している母親の情報源

としての信頼性を利用したこと，④判定に特別の技術や機器を必要としないので安価で医療経済学的に有効なこと，⑤ビタミンK欠乏性出血性疾患の予防に役立ちうること，⑥胆道閉鎖症以外に先天性胆道拡張症，新生児肝炎，アラジール症候群などの胆汁うっ滞性疾患の早期発見およびビタミンK欠乏性出血症の予防も可能であること，⑦胆道閉鎖症の手術成績の良い小児外科医の紹介が可能であること，⑧便色カードを配ること自体が胆道閉鎖症という稀少疾患のキャンペーン手段であることだった。

一方，短所は，①便色スケールの色の品質保持を印刷工の勘と経験に依存すること，②便色3番と4番の色調差が大きいのでそれらの中間の便色が必要であること，③1カ月健診受診後に発症する淡黄色便への対処が遅れる可能性があること，④便色カードを妊娠届提出時に母子健康手帳に挟んで渡すので，1カ月健診受診時にはカードをなくすなどインパクトが低下すること，⑤医師といえども胆道閉鎖症の患児を診たことのない場合もあって，便色カードを配るだけでは十分な効果は得られず，地道な啓発活動が必要なことであった。

Ⅶ．新版便色カード法の開発

便色カードに印刷される便色の品質管理は，胆道閉鎖症等の早期発見のうえで非常に重要である。私どもは2010年，第二版の便色カードを作成するにあたって，新しく撮影した胆道閉鎖症患児および生後1カ月の健常乳児の便をコンピューター処理し，色調を定量化した。またPDFファイルの一種であるPDF/X-1aファイルをデータフォーマットして印刷会社が指定すべき印刷用データを添付し，Japan Color 2001 Coated印刷規準で所定の用紙を使用した。これにより，便色スケールを最小限の誤差範囲で印刷することを可能にし，色調の標準化を図った。さらに初版便色カードの3番と4番の中間色が新版の4番に相当するようにした（図4）。

Ⅷ．新版便色カードの使用法

以下に，保護者（母親）への説明法を述べる。

1．使用方法

日中の明るい部屋で，オムツについた児の便に便色カードを近づけて色を見比べてください。カードの右側の部分をキリトリ線で切り取ると比べやすくなります。夜間でも昼光色の明るい照明の部屋で比べるなら大丈夫です。いずれの場合にもオムツの周囲に，色彩感覚に影響を与えるような派手な色のものを置かないでください。そしてオムツを交換する時などに，必ず便に便色カードを近づけて色を見比べて，もっとも近いと思う便色番号を記録してください。

便色カードには便色を見比べた結果の記録欄が3つあり，生後2週，生後1カ月，生後1～4カ月に，便色にもっとも近いと思う便色番号を，必ず3回ともカードに記入してください。生後1～4カ月と幅を持たせてありますが，生後2カ月がお勧めです。胆道閉鎖症の大部分の患児が生後2カ月までに淡黄色便を出すからです。

2．便色の判定後の対応

便と便色カードの色を見比べて，もっとも近いと思う便色番号を判定するとき，重要なのは以下の場合です。

① 1番～3番のうちのどれかに近い場合→1日も早く，その便を持参して，1カ月健診を担当する予定の医師を受診して，便と便色カードの色を見比べてもらいましょう。すでに1カ月健診が終わっている場合には，健診を担当した医師または小児科専門医が常勤する病院の小児科を受診してください。

② 4～7番に近い場合→4番以上ならば

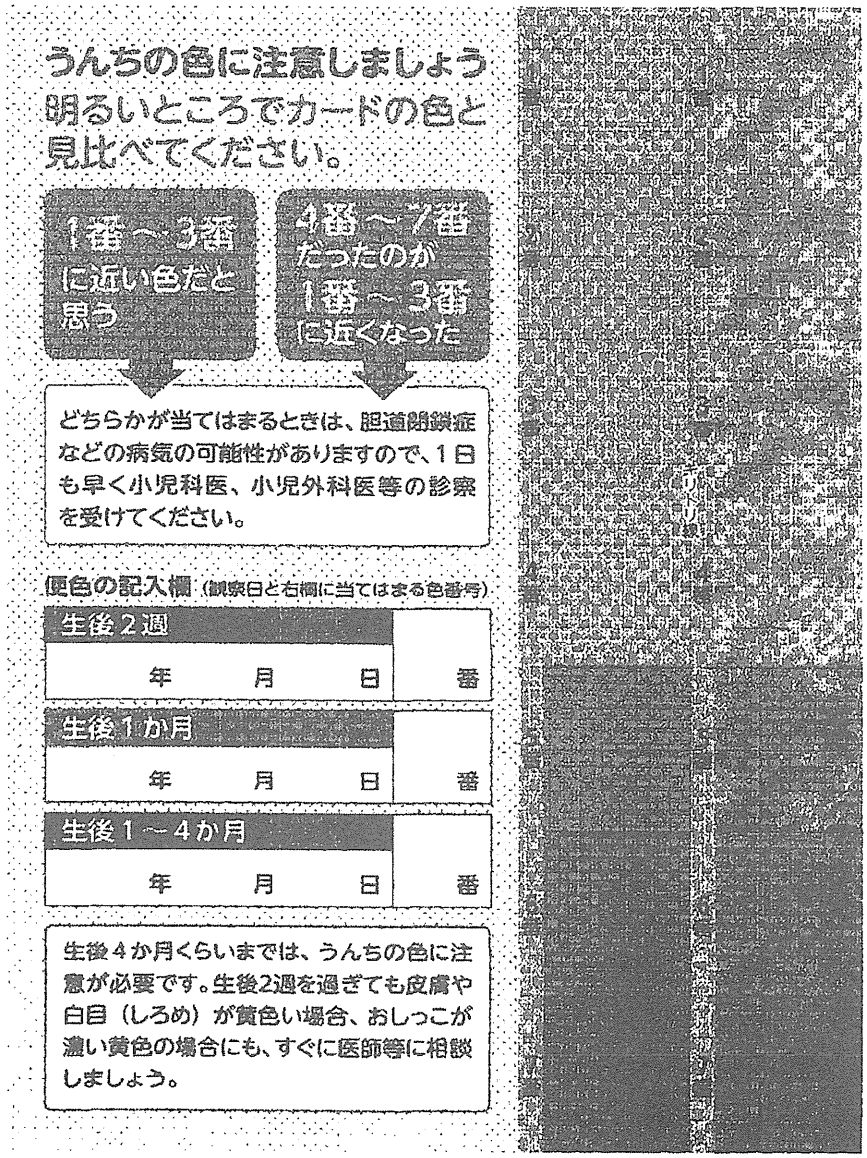


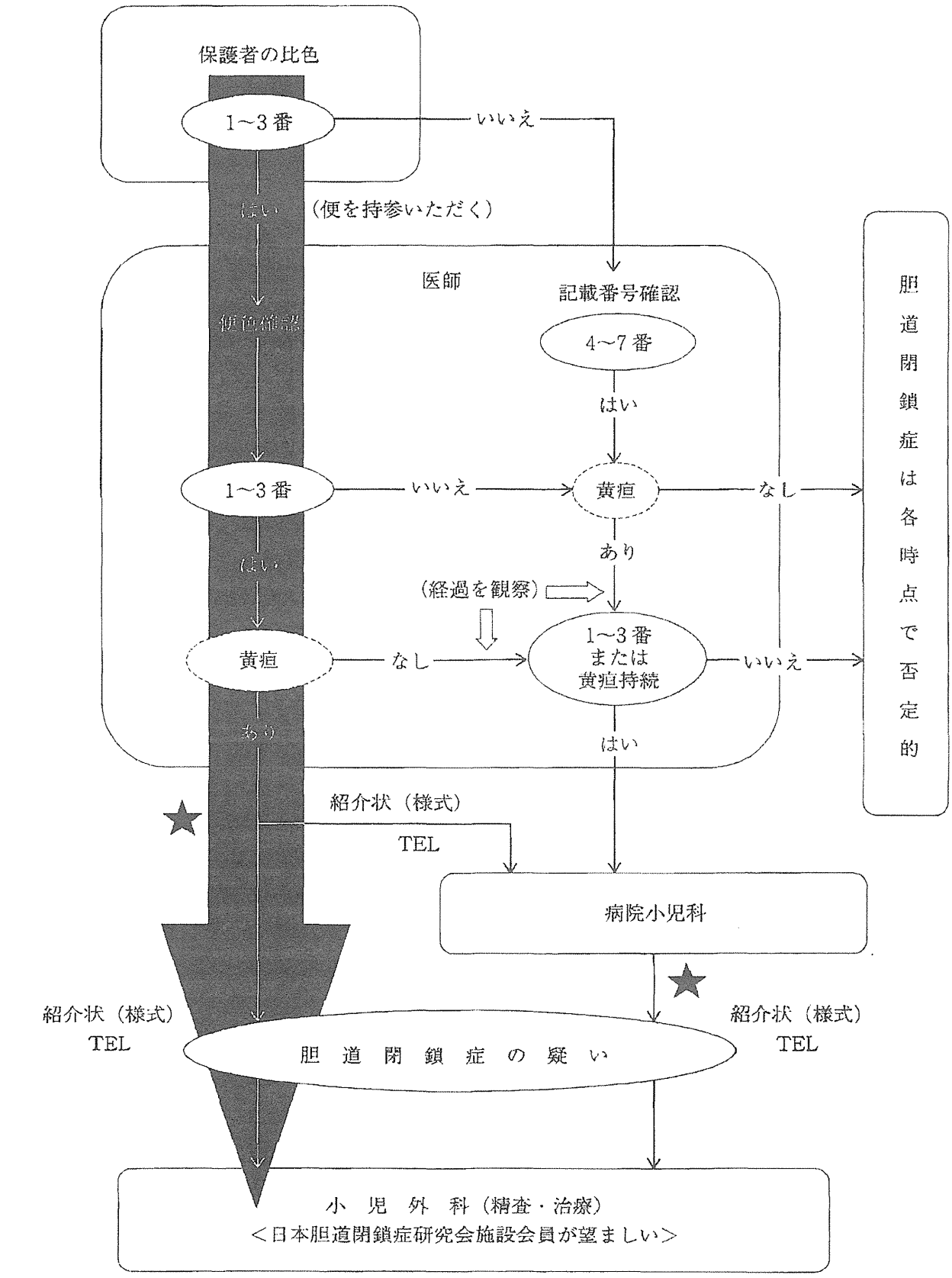
図4　全国的スクリーニングで使用される便色カード
（実物を添付する）

安心というわけではありません。その後，便色がうすくなって1～3番に近づくかどうかに注目してください。1～3番に近づいてきたと思ったら，その便を持参して，医師に見てもらいましょう。反対に4番から5～7番に近づく場合は，その時点で胆道閉鎖症の可能性はまずありませんが，生後5カ月になるまでは便色チェックを続けてください。

③　医師を受診する場合

医師や看護師と便色について話す時には，必ず便色番号をお伝えください。例えば「うちの子のうんちが3番なんです」というように伝えてください。同じ黄色といってもイメージする色は人によって異なるからです。それからできる限り，便のついたオムツを持っていき，医師に便と便色カードの色とを見比べてもらいましょう。時間が経過すると便色が変化するので，なるべく新しい便を持っていきましょう。

以上のスクリーニングのフローチャートを図示する（図5）。



★濃い黄色尿があればより確実！

図5　スクリーニングのフローチャート

おわりに

私ども小児科医，小児肝臓内科医は，長年にわたって胆道閉鎖症患児の早期発見に努めてきた。私が便色カードのアイデアを思いついたのは約20年前，1カ月健診で乳児の黄疸を推定するのに，イクテロメーターを使っていた時だった。便色を色の名前で表現すれば人が思い浮かべる色は十人十色である。母子健康手帳に便色を記入するアイデアは失敗だった。そこで便色スケールに番号を付けることを考えた。便色カードは栃木県をはじめ9つの自治体に普及して行った。やがて10年に一度の母子健康手帳の大改訂が平成24年度から行われたこと，改訂班の先生方，厚生労働省母子保健課の皆様をはじめ多くの方々のご理解を得て，母子健康手帳への便色カードの綴じ込みが実現した。母子健康手帳はわが国で生まれるほとんどすべての児に配布される。そして出生児の大部分が1カ月健診を受ける。これは胆道閉鎖症の全国的スクリーニングの開始を意味していた。しかし問題はすべて解決したわけではない。4番の便を出す児の取り扱いは簡単ではない。また便色カードの印刷は各自治体に任されており，その色の品質保持は容易ではない。啓発活動の必要性は消えたわけではないなど今後の検証が必要である。

これまでにご理解とお力添えをいただいた方々にこの場を借りて深謝申し上げるとともに，今後ともよろしくご指導をお願いいたします。

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☆　☆　☆　☆　☆　☆

accurate information on prognosis is often difficult to obtain in this condition.

Conclusions

In general, CBT are associated with poor prognosis and only limited information is available at present due to a lack of sufficient cases. Diagnosis during fetal life is difficult. It is important to extensively evaluate the tumor on imaging (location, size and features) and clinical features (gestational age at diagnosis, complications) and select the most appropriate management of pregnancy and the perinatal treatment based on consultation with various specialists. Accumulation of further data is important to clarify the entire clinical picture and establish a management system for this condition.

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Vincristine, actinomycin D, cyclophosphamide chemotherapy resolves Kasabach–Merritt syndrome resistant to conventional therapies

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Key words infant, kaposiform hemangioendothelioma, Kasabach–Merritt syndrome, vincristine, actinomycin D and cyclophosphamide therapy.

When kaposiform hemangioendothelioma (KHE) is accompanied by Kasabach–Merritt syndrome (KMS), it may result in considerable morbidity and mortality.[1,2] The usual treatment for KHE associated with KMS of the extremities includes the use of steroids, coil embolization, radiation therapy and interferon-α. Recently, vincristine (VCR) has also been reported to be effective to control the coagulopathy in KMS.[2–5] In the present case, KMS was resistant to conventional therapies, and so we elected to use VCR monotherapy. Several courses of VCR monotherapy were insufficiently and transiently effective, and the consumptive coagulopathy recurred. Therefore, we decided to treat this patient using combined vincristine, actinomycin D and cyclophosphamide (VAC) therapy. After four cycles of VAC, KMS caused by the left arm hemangioma finally resolved and there has been no recurrence for 6 years. In this case, VAC therapy was effective after failure of repeated VCR monotherapy.

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Case report

A male infant, born at full term by spontaneous vaginal delivery, was noted to have a large hemangioma of the left arm. He presented with anemia and thrombocytopenia at 1 month of age, and was diagnosed with KMS. The patient was referred to National Center for Child Health and Development for treatment of KMS at 2 months of age. First-line systemic therapy with corticosteroids was initiated (prednisolone 2 mg/kg per day) with simultaneous irradiation (10 Gy in five fractions), but it did not affect the tumor size or platelet counts. Subcutaneous injections of 1–3 × 10^6 (U/m^2 body surface area) of interferon-α for 1 month and mega-dose methylprednisolone therapy were then attempted, which also failed to improve KMS. At this stage the patient required 2 mg/kg per day of corticosteroids, and also needed frequent platelet transfusions to control bleeding. Transcatheter

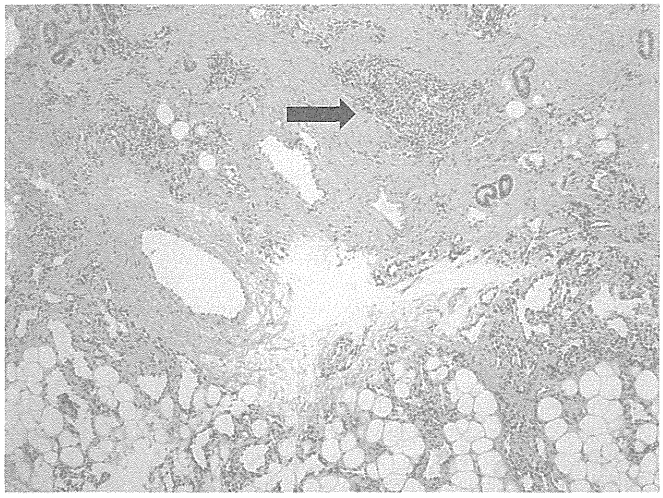

Fig. 1 Histopathology showing kaposiform hemangioendothelioma. The capillary vessels are diffusely proliferating in the fat tissues, and there is evidence of dense hyperplasia of the spindle shape cells (arrow).

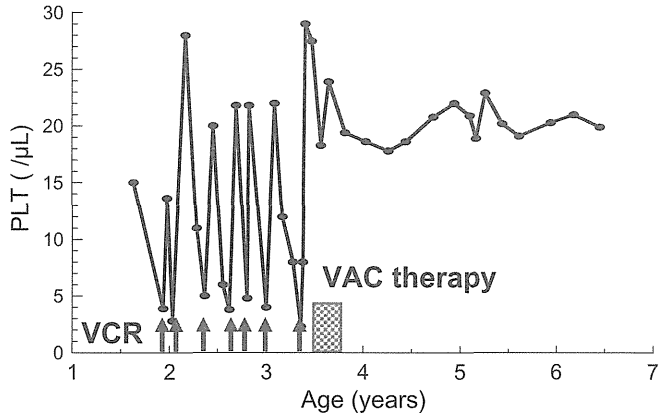

Fig. 3 Platelet counts after vincristine (VCR) or vincristine, actinomycin D and cyclophosphamide (VAC) therapy. VCR was dramatically effective for Kasabach–Merritt syndrome (KMS) but the effect was transient; the tumor showed regrowth and platelet counts repeatedly decreased. After eight courses of VCR monotherapy, the patient was treated with five courses of VAC. Remission of KMS was achieved for >4 years.

embolization of the feeding artery under general anesthesia was attempted three times. This resulted in a transient increase in the platelet counts. KMS relapsed within 2 weeks after the embolization. A biopsy showed that capillary vessels were diffusely proliferating in the fat tissues, and there was evidence of dense hyperplasia of spindle-shaped cells consistent with KHE, which frequently causes KMS (Fig. 1).[1,6–8]

Considering that the therapeutic effects of steroids, interferon-α, radiation, and embolization therapy were limited in the present case, we decided to start VCR. VCR was given weekly at a dose of 1.5 mg/m^2 (body surface area). After 8 weeks of VCR injections, the rate of platelet consumption gradually decreased, and platelet transfusions were no longer required (Fig. 2). After 11 cycles of VCR therapy, platelet counts increased up to 200 000/μL and were maintained at that level for a few months without any treatments. The tumor showed regrowth, however, and platelet counts decreased again 4 months after cessation of VCR therapy (Fig. 3). VCR monotherapy was again applied for recurrent KMS. In this situation, the platelet counts transiently increased after several episodes of VCR, but they gradually decreased after cessation of VCR therapy. After repeating seven doses of VCR monotherapy, at the age of 3 years it was decided to convert to a combination therapy of vincristine, actinomycin D, and cyclophosphamide (VAC). The VAC regimen included vincristine at 1.5 mg/m^2 on day 1, actinomycin D at 0.015 mg/kg on days 1–5 and cyclophosphamide at 10 mg/kg on days 1–3. During VAC therapy there were no serious side-effects. After four cycles of VAC therapy, KMS caused by the left arm hemangioma was finally resolved and there has been no recurrence for 6 years (Figs 3,4).

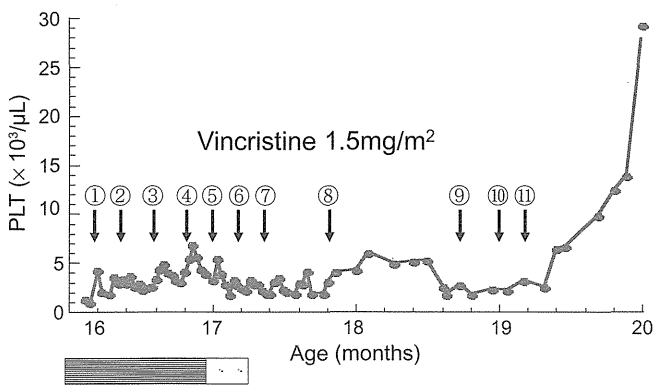

Fig. 2 Platelet (PLT) counts after vincristine (VCR) therapy. PLT infusions were required every day until the fifth VCR injection. After eight courses of VCR the patient did not require PLT infusions, and the PLT count increased from 40 000 to 250 000/μL.

Discussion

When KHE is accompanied by KMS, it may result in considerable morbidity and mortality. In the present case KMS was treated with steroids, coil embolization, radiation therapy and interferon-α, but these therapies were totally ineffective. Biopsy indicated KHE, which often causes life-threatening KMS.[9] Several reports have recently shown VCR to be effective for controlling the decreased platelet counts and potential mortality associated with KMS.[3–6,9–11] In addition, Haisley-Royster *et al.* reported that all four patients in whom KMS relapsed after a first course of VCR therapy, were successfully treated with second courses of VCR.[9] In contrast, the present patient had a relapse of KMS after several doses of VCR monotherapy.

Hu *et al.* reported that combined VAC therapy was effective for intractable KHE associated with KMS, which was resistant to corticosteroid therapy.[7] Because of toxicity considerations, such as veno-occlusive disease, hemorrhagic cystitis, pancytopenia