using primers specific for the S, pre-S, pre-C/C, and X regions. The sensitivity of our nested PCR analysis used in this study has been described previously [16]. As shown in Table 1, amplification of HBV-DNA was not observed in the serum of anti-HBc positive individuals using any primer sets. In contrast, the liver tissues of 15 of the 21 (71.4%) anti-HBc positive donors were positive for HBV-DNA. These data are consistent with previous data indicating that the anti-HBc positive healthy individuals have latent HBV infection in the liver [16–21]. The lymph node samples of 11 of the 21 (52.4%) anti-HBc positive individuals were also HBV-DNA positive in the three repeated assays (Table 1). Moreover, three individuals positive for anti-HBc but negative for HBsAg also had HBV-DNA in their PBMC. These three were also positive for HBV genomes in their liver, although they lacked viral DNA in their lymph nodes from the hepatoduodenal ligament. HBV genomes were not detected in any of the liver or serum samples of donors without HBV-related serological markers. These findings suggest the presence of HBV genome in lymphatic tissues of individuals who have latent HBV infection in the liver.

3.2. Analyses of the replicative form of HBV in the lymphatic tissues

To clarify whether HBV infection was maintained as an episomal form in the extrahepatic tissues, we examined the presence of HBV replicative forms, including cccDNA and intermediate RNA [35,36], in the lymph nodes of five anti-HBc positive donors who were positive for HBV genome sequences in their lymphatic tissues. For the selective detection of the cccDNA form of HBV, we performed cccDNA-specific PCR amplification accompanied by mung bean nuclease treatment (Fig. 1A) [16,29]. We first confirmed that a faint signal derived from the X region in the serum sample with a high level of HBV-DNA titer had completely disappeared after the nuclease digestion, whereas the S sequences were amplified in the same sample after the treatment with the endonuclease (Fig. 1B). This effect of endonuclease indicated the specificity of the digestion method for rcDNA in virions and agreed with previous reports [15,29]. As shown in Fig. 2A, both the liver and the lymph node tissues of all five anti-HBc positive donors were positive for HBV-DNA by conventional PCR assay using a primer set for the S region, which is conserved in both cccDNA and rcDNA molecules. Selective amplification of cccDNA detected HBV-derived cccDNA-specific bands of the expected size (658 bp) in the liver tissue of all five donors. In contrast, the amplified products originating from HBV-cccDNA were detected in none of the lymph node samples of these five donors in three replicate assays. Similar results were obtained by highly sensitive amplification of cccDNA by PCR accompanied by a single cut of cccDNA by EcoRI treatment (Fig. 2B). To further examine whether active transcription and replication were present in the lymphatic tissues, we performed RT-PCR followed by Southern blotting assay to detect the pregenomic

Table 1
Serological status and the results of PCR amplification of HBV-DNA in the various tissues of anti-HBc positive donors

Case number	Sex	Age (year)	HBsAg/ anti-HBs	anti-HBc	HBeAg/ anti-HBe	HBV-DNA			
						LN	Liver	Serum	PBMC
1	F	45	−/+	+	−/+	+	+	−	−
2	M	42	−/+	+	−/+	+	+	−	−
3	F	48	−/+	+	−/+	−	−	−	−
4	F	50	−/+	+	−/+	−	−	−	−
5	M	35	−/+	+	−/+	−	+	−	−
6	F	54	−/−	+	−/−	+	+	−	−
7	M	52	−/+	+	−/−	−	−	−	−
8	F	35	−/−	+	−/−	−	−	−	−
9	M	40	−/+	+	−/+	+	+	−	−
10	M	37	−/+	+	−/+	+	+	−	−
11	M	63	−/+	+	−/−	−	−	−	−
12	F	34	−/−	+	−/−	+	−	−	−
13	F	42	−/+	+	−/+	+	+	−	−
14	F	38	−/+	+	−/+	−	+	−	−
15	M	29	−/+	+	−/+	−	+	−	+
16	M	53	−/−	+	−/+	+	+	−	−
17	M	37	−/+	+	−/+	+	+	−	−
18	M	48	−/+	+	−/−	−	+	−	+
19	M	24	−/+	+	−/−	+	+	−	−
20	M	53	−/+	+	−/−	−	+	−	+
21	F	52	−/+	+	−/+	+	+	−	−

LN, lymph node; PBMC, peripheral blood mononuclear cells; HBsAg, hepatitis B surface antigen; anti-HBs, antiboby to HBsAg; anti-HBc, antibody to hepatitis B core antigen; HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg.

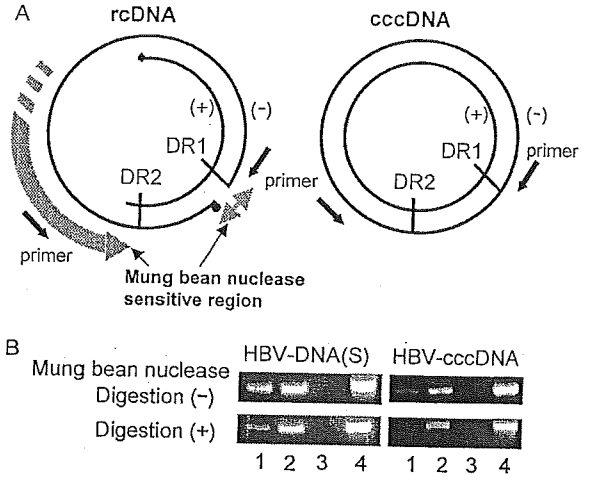

Fig. 1. Detection of HBV cccDNA using mung bean nuclease digestion followed by PCR amplification. (A) The structure of HBV cccDNA and relaxed circular DNA (rcDNA), and mung bean nuclease sensitive region in rcDNA. Mung bean nuclease cleaves a part of the single stranded region in the minus strand. PCR primers for the detection of cccDNA were not expected to amplify the HBV rcDNA sequences across the gaps after the digestion with mung bean nuclease. (B) PCR amplification of the S region (left panel) and X region (right panel) after the selective digestion of HBV rcDNA molecules (DNA extracted from the serum of HBsAg-positive case). The digestion of mung bean nuclease was performed prior to nested-PCR with primers across the nick region of rcDNA (X region). Upper panel, mock digestion; lower panel, mung bean nuclease digestion; lane 1, serum of HBsAg-positive case; lane 2, liver tissue of HBsAg-positive case; lane 3, liver tissue of donor without any HBV serological markers; lane 4, expression plasmid of the HBV-DNA encoding the S and X region.

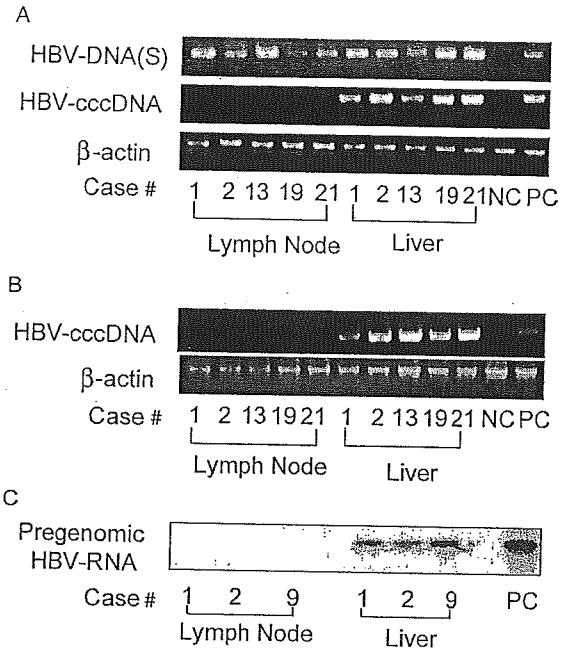

Fig. 2. Detection of HBV cccDNA and pregenomic RNA in lymph nodes and liver tissues of anti-HBc positive healthy donors. (A) HBV-DNA was amplified using primer sets for the S region (upper panel) or the primers specific for cccDNA after the selective digestion of HBV rcDNA molecules by mung bean nuclease (middle panel). The figure shows representative results of PCR amplification using DNA samples extracted from the lymph nodes and livers of donors #1, #2, #13, #19, and #21. NC, liver tissue of donor without any HBV serological markers; PC, liver tissue of HBsAg-positive case. (B) DNA samples extracted from the lymph node and liver tissues were digested with EcoRI to linearize the cccDNA molecule, followed by PCR amplification using the primers specific for cccDNA, as described above. The figure shows representative results of PCR amplification using DNA samples extracted from the lymph nodes and livers of donors #1, #2, #13, #19, and #21. (C) Total RNA was extracted from the lymph node and liver tissues of three healthy donors positive for anti-HBc. One-step RT-PCR for amplification followed by Southern blotting analysis targeting the S region of HBV RNA was carried out. Total RNA extracted from HBsAg-positive liver tissue was used as a positive control. Lanes 1–3, lymph nodes of donors #1, #2, and #9; lanes 4–6, liver tissues of donors #1, #2, and #9; lane 7, HBsAg-positive liver.

HBV-RNA. Total RNA extracted from both the lymph node and the liver was available in three anti-HBc positive donors for further analyses. As shown in Fig. 2C, the positive signals at the expected size representing HBV-RNA were detectable in the liver tissues of all three anti-HBc positive donors tested. However, no amplification of the HBV-RNA was observed from the total RNA samples extracted from the lymph nodes of these individuals (Fig. 2C). These findings suggested that the HBV genomes detected in the lymph nodes of anti-HBc positive individuals did not contain the replicative form of HBV.

3.3. The presence of the integrated form of HBV in the lymphatic tissues

As HBV replicative forms were not detected in lymphatic tissues of anti-HBc positive individuals, we reasoned that the HBV genome might be present as an integrated form in the extrahepatic tissues. To address this question, we separated the DNA from the lymph node and liver tissues of anti-HBc positive individuals into two fractions according to their molecular sizes, as described previously [16]. Human β-actin and p53 gene sequences were amplified from the HMW fractions of all subjects, revealing that this fraction contained host chromosomal DNA (Fig. 3A for β-actin, data not shown for p53). In the liver tissues, two of six cases were positive for HBV-DNA in the HMW host chromosomal DNA fraction (Fig. 3A). Interestingly, HBV sequences were detected in three of six HMW fractions of DNA samples extracted from lymphatic tissues (lymph nodes of cases #13, #17, and #21), suggesting that the HBV genome in the lymph nodes of anti-HBc positive individuals is most likely present as an integrated form.

To further examine the presence of HBV integration in lymphatic tissues, we performed inverse-PCR-based amplification of HBV-DNA to identify the host-viral junction sequences. We selected the S region of HBV as the target sequences of inverse-PCR analyses because amplification of this region shows the highest sensitivity for detecting HBV sequences in lymphatic tissues of anti-HBc positive

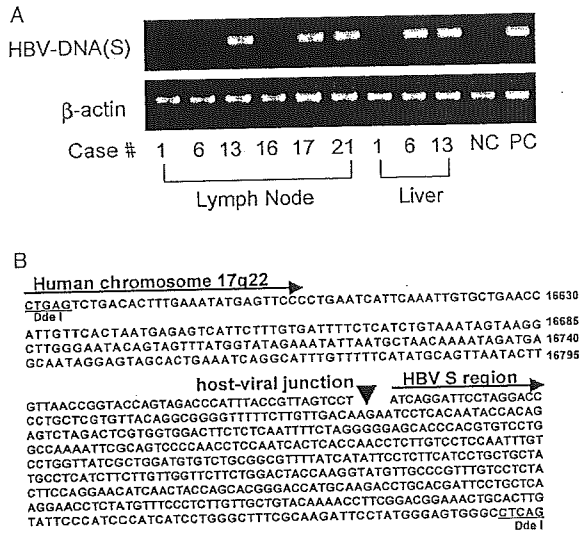

Fig. 3. Detection of HBV integration in the lymph nodes of anti-HBc positive donors. (A) Detection of the HBV genome in a high molecular weight (HMW) fraction of extracted DNA. HMW fractions of extracted DNA from the lymph nodes and liver tissues of anti-HBc positive donors (donors #1, #6, #13, #16, #17, and #21) were separated by a modification of alkali-lysis procedure, followed by amplification of the S region of HBV-DNA using nested PCR (upper panel). To show the presence of the genomic DNA in the HMW fraction, amplification of β-actin gene was carried out using the same samples as templates (lower panel). (B) HBV-host junction sequence in the extracted DNA from the lymph node of donor #21. Host flanking DNA was located in the sequence of chromosome 17 (GenBank gi: 15281290). The HBV-DNA sequence covers from nucleotide 43 of the surface gene. The restriction enzyme DdeI restriction sites are underlined.

individuals (Table 2). In the lymph nodes of one of three cases (case #21), one visible DNA signal was observed, which showed the different sizes from the common fragments found in all three samples, suggesting a unique HBV integrant in the inversely-amplified PCR product. The nucleotide sequence analysis in this specifically amplified fragment contained both viral and human genome sequences. As shown in Fig. 3B, the human DNA sequence located in chromosome 17q22 was identified as a host flanking sequence, which was connected with the S region of HBV-DNA. Together, these data suggest the presence of HBV integration in host chromosomal DNA of lymph nodes of anti-HBc positive latent HBV carriers.

Table 2
Detection of HBV-DNA in the lymph node and liver tissues of 21 anti-HBc positive donors

	Number of HBV-DNA positive subjects			
	S	pre-S	pre-C/C	X
LN	12/21	11/21	4/21	0/21
Liver	15/21	13/21	10/21	6/21

LN, lymph node; S, surface; pre-C/C, pre-core/core.

4. Discussion

Although several previous studies have reported the presence of HBV genomes in PBMC, it is still controversial whether HBV exists as an episomal form and replicates in extrahepatic tissues [3–15]. In this respect, it should be noted that most previous studies examined the PBMC of HBV carriers positive for HBsAg, who normally have HBV-DNA in their serum. Thus, it is possible that the detected viral genomes in PBMC were derived from viruses circulating in the serum or adsorbed to the PBMC. For example, Kock et al. reported that HBV particles can bind tightly to various types of cells so that attached viruses cannot be washed away and remain detectable in culture for many days [15]. To exclude the possibility of contamination of the circulating HBV-DNA, we examined PBMC and lymph nodes from LDLT donors positive for anti-HBc but negative for HBsAg. We have previously shown that HBV-DNA is rarely detected in the serum of these donors, despite their latent infection with the episomal form of HBV which is associated with ongoing viral replication in the liver [16,21]. Therefore, we first confirmed by PCR that HBV-DNA could not be detected in the serum in the anti-HBc positive donors to exclude the possible contamination by serum HBV-DNA in extrahepatic tissues. Our data demonstrated clearly that HBV-DNA is present in lymphatic tissues and PBMC of anti-HBc positive latent HBV carriers. Our data agree with those from a previous report showing identification of HBV-DNA sequences in PBMC of liver transplant recipients who were serum HBV-DNA negative by PCR analysis [37].

Although HBV-DNA could be detected in both the lymph nodes and PBMC of our subjects, we found no evidence of viral replication in tissues of any individual with latent HBV infection. The lack of cccDNA and pregenomic forms of RNA in the lymph nodes and PBMC strongly suggests that HBV can exist in lymphatic tissues without viral replication or proliferation. These findings are consistent with previously reported clinical outcomes in liver transplant patients, in which none of the recipients who were positive for anti-HBc but negative for HBsAg and who had HBV genomes in their liver tissues had acquired HBV reactivation after total removal of the infected liver through liver transplantation [28]. It may be emphasized that these recipients generally receive intense immunosuppressive therapy; nevertheless, none of them developed HBV reactivation after LDLT. Our results contrast with other previous studies [4–6,14]. For example, cccDNA and pregenomic forms of RNA were detected in PBMC of patients negative for HBsAg but positive for HBV-DNA in the serum [14]. As discussed above, the discrepancies between our results and those from other reports may be related to the presence or absence of circulating viral particles in the patient's serum. A considerable number of viral particles circulating in the serum was shown to contain viral RNA rather than DNA, suggesting that previous

observations of the presence of HBV infection in PBMC could be explained by adsorbed virus [15]. Since Soussan et al. showed recently that a singly spliced HBV-RNA encodes a novel HBV protein in vivo [38], there is room for further investigation to clarify whether HBV-spliced mRNA can be present in extrahepatic tissues.

Our findings also suggest the presence of integrated HBV-DNA in lymph node samples of anti-HBc positive carriers. To obtain direct evidence of HBV integration into host genomes, we used an inverse-PCR-based method using two pairs of inverse primers around the S region of HBV-DNA. It has been reported that many of the viral-host junctions cluster near the DR1 region of HBV sequences [39,40]. However, we found that amplification of the S region was the most sensitive method to detect the minimum amount of HBV genome present in lymphatic tissues of anti-HBc positive individuals. We targeted this region in the inverse-PCR analyses, and identified HBV integrants and flanking host sequences located in chromosome 17q22 in the lymph node of one case with anti-HBc. Our data agree with those in recent reports that observed viral integration in PBMC samples from patients with HBV-related acute and chronic liver disease [41,42]. However, detection of integrated viral DNA by inverse-PCR does not imply the clonal expansion of HBV in lymph nodes, and the question of whether the viral integration reflects the prior infection of proliferating bone marrow cells or the stimulation of PBMC expansion is still unanswered [3,42].

In conclusion, our data suggest that lymph nodes and PBMC do not support active replication of HBV in latent HBV carriers who are positive for anti-HBc but negative for HBsAg, in whom the ongoing viral replication occurs in the liver. Instead, HBV may persist as integrated forms in their extrahepatic tissues. Further analysis is needed to determine the molecular status of HBV infection in extrahepatic tissues of highly viremic HBV carriers.

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Duct-to-duct biliary reconstruction in pediatric living donor liver transplantation

Okajima H, Inomata Y, Asonuma K, Ueno M, Ishiko T, Takeichi T, Kodera A, Yoshimoto K, Ohya Y. Duct-to-duct biliary reconstruction in pediatric living donor liver transplantation.
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Abstract: The results of duct-to-duct biliary reconstruction in six pediatric patients who received a living donor liver transplant aged from 2 months to 11 yr old are reported. The graft was either entire or a part of the left lateral segments. The orifice of the bile duct of the graft was anastomosed to the recipients' hepatic duct in an end-to-end fashion by interrupted suture using 6–0 absorbable material. A transanastomotic external stent tube (4 Fr) was passed through the stump of the recipients' cystic duct. Mean time for reconstruction was 24 min. All the recipients survived the operation and reinitiated oral intake on postoperative day 3. There were no early biliary complications. One 5-yr-old boy suffered from an anastomotic stenosis 9 months after transplantation. He underwent re-anastomosis by Roux-en Y (R-Y) procedure and recovered uneventfully. Duct-to-duct anastomosis in pediatric living donor liver transplantation has benefits while the complication rate is comparable to R-Y reconstruction.

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In pediatric liver transplantation, both cadavericand live-donated cases, R-Y hepatico-jejunostomy is often performed for biliary reconstruction because of the prevalence of BA. With the recent expansion of LDLT to adults, DD anastomosis for biliary reconstruction in LDLT is becoming more common (1–4). In pediatric LDLT even in the patients without BA, the main procedure is still the R-Y. However, there are benefits to perform a DD anastomosis, such as not having to manipulate the gastrointestinal tract, a short operative time and easy assess to the anastomosis using retrograde catheterization with an endoscope. We report our results of DD biliary reconstruction in six pediatric patients, including a young infant.

Patients and methods

Six children (four boys and two girls, aged from 2 months to 11 yr old) underwent LDLT with DD biliary reconstruction (Table 1). The 2-month-old patient, a girl, received a part of the left lateral segment from her mother who had an incompatible blood type. The others received complete left lateral segments from one of their parents with identical blood type (Table 2).

Abbreviations: BA, biliary atresia; DD, duct-to-duct; HTK, Histidine-tryptophan-ketoglutarate; LDLT, living donor liver transplantation; PTCD, percutaneous transhepatic cholangio-drainage; R-Y, Roux-en Y.

Operative procedure

The biliary tree of the donor was evaluated by preoperative three-dimensional CT cholangiography and intraoperative cholangiography. HTK solution was used for perfusion and preservation of the graft. Each graft had one biliary tract orifice, which was 2–4 mm in diameter. During the hepatectomy of the recipient, the bile duct was transected as proximal as possible, usually, at the level of each hepatic duct. The gallbladder was resected, but a long segment of the cystic duct was left as the entry site of the transanastomotic stent tube. After completion of the anastomosis of hepatic vein and portal vein, the graft was re-perfused before the hepatic artery was microsurgically reconstructed. The connective tissue around the recipient's common duct was preserved as much as possible, although the whole supra-pancreatic portion was dissected. The anastomotic orifice of the recipient's side was chosen according to the size of the graft bile duct. The common bile duct was used for three elder patients, and a branch patch was used for three younger patients. The blood supply of the stump of the common bile duct was confirmed by observing bleeding when making a small cut at the tip of the stump of the bile duct. Before

Table 1. Recipients' characteristics

Case	Age	Sex	BW. (kg)	Disease	Follow-up period	Complications
1	2 mo	F	5	FHF[a]	19 mo	(-)
2	1 yr	M	10	Byler's disease	2 mo	(-)
3	3 yr	M	9	Byler's disease	36 mo	(-)
4	5 yr	M	14	Hepatoblastoma	24 mo	stenosis
5	7 yr	M	26	Wilson's disease	3 mo	(-)
6	11 yr	F	24	Wilson's disease	6 mo	(-)

[a] FHF, fulminant hepatic failure

Table 2. Details of operative data

Case	Type of graft	GW/RBW ratio[a]	Diameter of bile duct	Time for reconstruction
1	monosegment	5.20	2.5 mm	25 min
2	left lateral	2.10	3.0 mm	35 min
3	left lateral	2.60	3.0 mm	35 min
4	left lateral	1.07	3.0 mm	20 min
5	left lateral	1.30	3.0 mm	35 min
6	left lateral	0.76	3.5 mm	18 min

[a] GW/RBW ratio, graft weight/recipient body weight ratio

the anastomosis, a 4 Fr stent tube was guided through the remnant cystic duct and out the distal end of the recipient's bile duct (Fig. 1). End-to-end anastomosis was carried out with 6–0 absorbable sutures using the interrupted technique. The sutures were tied outside of the lumen. After completion of the posterior wall, the stent tube was inserted 2 cm into the graft. The anastomosis was then completed and the tube passed out through the abdominal wall. The stent tube was kept in place for at least 3 months.

Postoperative result

The mean time for reconstruction was 24 min and ranged from 18 to 35 (Table 2). All six recipients recovered from the transplantation uneventfully. Oral intake was started on postoperative day 3 in all cases. There were no early biliary complications. A 5-yr-old boy suffered from an anastomotic stenosis at 9 months after transplantation. In this recipient, the stent tube was mistakenly removed at 4 wk after the transplant, instead of 3 months in our protocol. Anastomotic stenosis was diagnosed by endoscopic retrograde cholangiography (Fig. 2). An attempt at balloon dilatation by endoscopic intervention failed because the guide wire could not be placed though the stenosis. Intervention through the PTCD was also performed, but failed. Therefore, re-anastomosis by R-Y was performed. He recovered uneventfully and is doing well 30 months after transplantation. None of the other patients showed signs of early or late biliary complications with a mean follow-up period of 17 months.

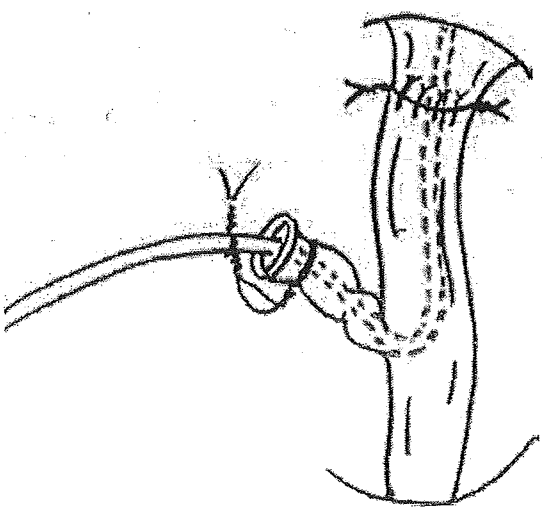

Fig. 1. A 4 Fr stent tube was inserted through the remnant cystic duct and into the recipient bile duct. End-to-end anastomosis was carried out with 6–0 absorbable suture using the interrupted technique.

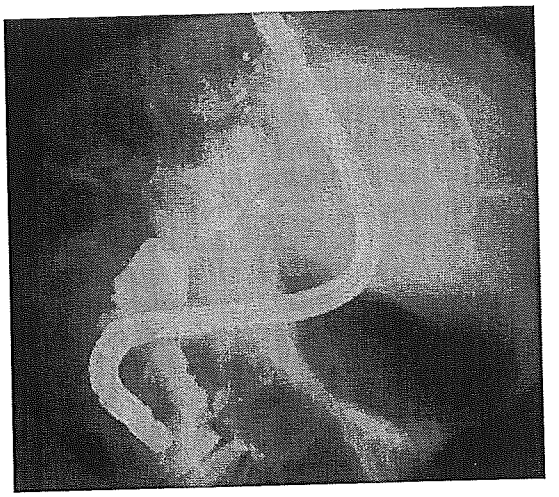

Fig. 2. Endoscopic retrograde cholangiography showed anastomotic stenosis on 5-yr-old boy at 9 months after transplantation.

Discussion

The incidence of bile duct complications in pediatric living related liver transplantation using a R-Y reconstruction is reported as high as 14% (5). Bile leakage because of anastomotic dehiscence in R-Y reconstruction is particularly serious as it may cause fatal peritonitis. Theoretically, DD anastomosis has benefits when it is compared with the R-Y procedure. These include no need for intestinal manipulation, a short operative time, a more physiologic bilioenteric continuity, less severity in case of biliary leakage and an easy assess to the anastomosis through retrograde catheterization using an endoscope. More than 75% of pediatric LDLT patients have BA and R-Y is the most common procedure in biliary reconstruction. However, in the patients with metabolic diseases or fulminant hepatic failure, the bile duct is available for reconstruction. In this series, all the children were able to start oral intake on postoperative day 3, a few days earlier than with the R-Y procedure in our institution. The mean time for D-D

reconstruction was 27 min. Because it was not necessary to make a R-Y limb, operative time was shorter. There were no early biliary complications in this series. In case of major leakage at the hepaticojejunostomy, external diversion of R-Y limb may be necessary to avoid a fatal outcome. We consider that postoperative care without such a concern is a great benefit of D-D anastomosis.

A drawback of DD reconstruction is the higher risk of postoperative stricture, which is mainly caused by tension around the anastomotic site or by poor blood supply to the recipient bile duct (1, 2). The blood at the tip of the recipient's bile duct is provided by the intramural capillary network connected to the original artery in the intra-pancreatic portion (6). Therefore, significant tension or stretch of the bile duct may cause ischemia at the tip, and lead to subsequent stricture of the anastomosis. Release of the tension by the longer dissection is important as well as the preservation of the surrounding connective tissue. Another concern with DD reconstruction is the fragility. In the present series, the diameter and the thickness of the common hepatic duct of the 2-month-old girl was compatible with those of the graft bile duct.

In our series, the 5-yr-old boy experienced anastomoric stricture. Although re-anastomosis by R-Y was necessary in this case, it could be diagnosed by retrograde cholangiography with an endoscope which could not have been possible in a R-Y. The possibility of including an endoscope for diagnosis and treatment of biliary complications, is a definite advantage in DD anastomosis.

The use of the of the stent in the biliary reconstruction after liver transplantation has long been a debatable issue, and a clear conclusion is not available. A disadvantage to a prolonged external stent, is the mild disturbance of the quality of life. When there is poor blood supply or significant tension at the anastomosis, a longer period of stent placement may sustain a patient lumen in the process of healing, although there are no scientific data to support a prolonged stent placement. The fact that only one case of a late complication in this series was the patient who lost the stent earlier than scheduled may suggest the benefit of a prolonged stent placement, although, again, no conclusive data are available.

In conclusion, DD anastomosis has benefits and the results are comparable to R-Y reconstruction in pediatric LDLT recipients.

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Feasibility of Using the Cystic Duct for Biliary Reconstruction in Right-Lobe Living Donor Liver Transplantation

Katsuhiro Asonuma, Hideaki Okajima, Mikako Ueno, Takayuki Takeichi, Manuel E. Zeledon Ramirez, and Yukihiro Inomata

Duct-to-duct biliary reconstruction has been introduced in adult living donor liver transplantation (LDLT). In right-lobe grafts, however, the presence of two or three separated bile duct orifices is not rare and makes an alternative approach for reconstruction necessary. We used the cystic duct for one of the anastomoses in biliary reconstruction for 5 right-lobe living donor liver transplants with two separated ducts. Before the anastomosis, the inside lumen of the cystic duct was straightened with a metal probe. Two external drainage tubes were placed in all recipients, and posttransplant cholangiography through the tubes approximately one month after transplantation showed no leakage or stricture at any of the anastomotic sites. The drainage tubes were removed between 17 and 37 weeks after transplantation. All of the patients except one who died of chronic rejection have been doing well without any late biliary complications during follow-up periods ranging from 10 to 28 months after transplantation. In conclusion, our results indicate that biliary reconstruction using the cystic duct is feasible and safe for living donor liver transplantation and that external drainage tubes may be effective for prevention of complications. (*Liver Transpl 2005;11:1431-1434.*)

Biliary tract complications are some of the most frequent problems after living donor liver transplantation (LDLT).[1] In an effort to prevent the serious complications that can occur in hepaticojejunostomy, duct-to-duct biliary reconstruction, especially in right-lobe LDLT, has recently become widely accepted.[2-5] The biliary tree of right-lobe grafts, however, features many anatomical variations, with absence of the right hepatic duct reported in as many as 26% of 110 resected livers.[6] In many instances, two or three bile-duct reconstructions may therefore be necessary, and modified techniques for these situations have been employed.[7] In situations where the distance between orifices permits it, two orifices have been transformed into one. In other cases, the right and left hepatic ducts have been used for separate anastomoses. Furthermore, if the two orifices are far apart, combining a hepaticojejunostomy with a duct-to-duct anastomosis has been attempted.[2] In these special cases, a modified technique using the cystic duct for the reconstruction of one of the separated orifices of the bile duct is needed. Sue et al. reported successful use of the cystic duct for biliary reconstruction in three cases.[8] However, only two of the three cases underwent a double-biliary anastomosis, and the follow-up periods were relatively short. In the study presented here, we review 5 LDLT transplants performed with a double-biliary reconstruction technique that uses the cystic duct and the right hepatic duct for two separate anastomoses as well as two external biliary stent tubes. The efficacy of biliary reconstruction using the cystic duct with an external drainage tube was assessed during both short- and long-term follow-up periods after LDLT.

Patients and Methods

Between September 2000 and December 2004, 80 cases of living donor liver transplantation were performed at our institution. Left-lobe grafts were used in 45 cases and right lobes in 30. The remaining 5 cases underwent domino transplantation with whole-liver grafts. Duct-to-duct biliary reconstruction was performed for all of the right-lobe graft cases, 15 of whom had one hepatic duct, 15 had two, and none had triple orifices. At the back table, 8 double orifices were transformed into single ones. The other 7 cases needed two separate reconstructions, and for two of them the right and left hepatic branches of the recipient's hepatic duct could be used. The two orifices of the anterior and posterior branches of the graft bile duct were too far apart in the remaining 5 cases; however, the recipient's cystic duct was used for reconstruction of one of the orifices (Fig. 1).

The right and left hepatic ducts were dissected at the hepatic hilum during the recipient operation and cut separately to preserve the two small orifices of the bile duct. If the information obtained from the preoperative biliary computed tomography (CT) scan or intraoperative cholangiography suggested the presence of two separate orifices of the graft bile duct, the cystic duct including the neck of the gall bladder was preserved as long as possible during the recipient operation.

Abbreviation: LDLT, living donor liver transplantation.

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The stump of the cystic duct was tapered down to the size of the graft bile duct before reconstruction. We usually confirmed the arterial blood supply at the stump of the cystic duct by cutting the wall of the edge. Before the anastomosis, the spiral form of the inside lumen of the cystic duct was straightened by gently prodding it with a metal probe until it was dilated and entirely passable. Reconstruction was performed in an end-to-end fashion between the graft bile duct and the recipient hepatic duct or cystic duct with interrupted 6-0 PDS suture. Two 4-French polyethylene tubes, inserted via the left hepatic duct in one, via the cystic duct in one, and via the common bile duct in the other cases, were used for external drainage (Fig. 2). Cholangiography through both tubes was performed approximately one month after transplantation. Biliary complications were diagnosed clinically, biochemically, or radiologically.

Results

Patients' demographics are shown in Table 1. There were 5 males and one female with an age range from 18 to 58 years. The underlying diseases were hepatitis C with hepatocellular carcinoma in two patients, and hepatitis B, Caroli disease, and fulminant hepatic failure in one each. The distance between the orifice of the anterior branch and the posterior branch in the right-lobe grafts of all the patients was more than 1.5 cm. The cystic duct was anastomosed to the anterior branch in three and to the posterior branch in two. The right hepatic duct was used for all other reconstructions. There were no clinical signs of leakage during the early postoperative periods, and cholangiography performed around one month after transplantation did not show either leakage or stricture of the anastomotic sites (Fig. 3). The external biliary drainage tubes were removed between 17 and 37 weeks after transplantation. Patient 1 died of chronic rejection 13 months after transplantation without any signs of biliary complications throughout the entire postoperative course. Although

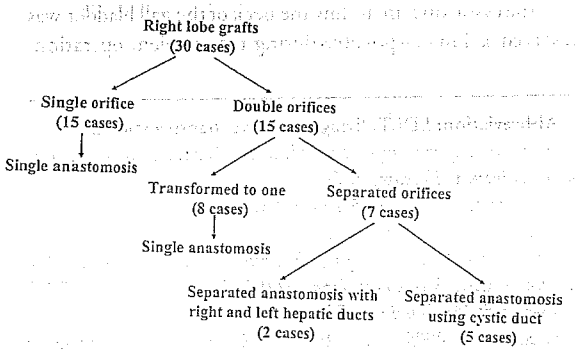

Figure 1. Modalities of duct-to-duct reconstructions for right-lobe grafts.

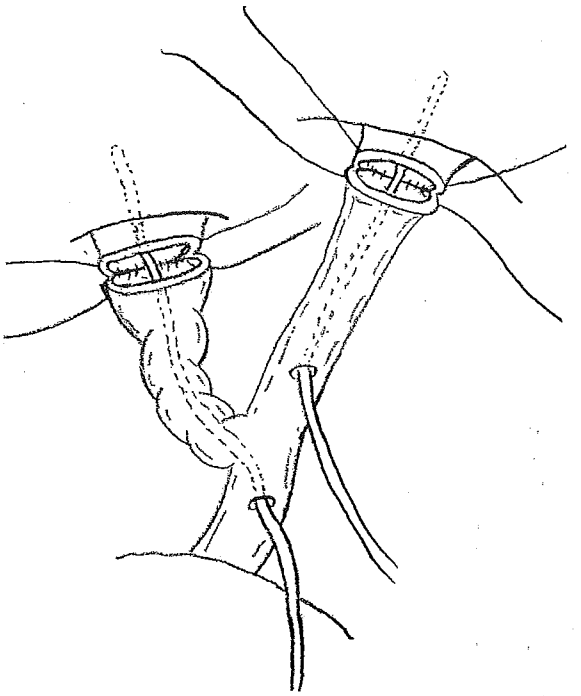

Figure 2. Schema of separated anastomosis of two bile ducts using the cystic duct and the placement of two external drainage tubes.

patients 2 and 3 suffered from recurrence of hepatitis C as evidenced by abnormal biochemical findings, they recovered with the aid of interferon and ribavirin therapy. Patient 5 exhibited hyperbilirubinemia due to rejection but recovered after administration of sirolimus. Follow-up periods ranged from 11 to 28 months (median 14 months). All patients but one are alive and doing well without any clinical signs of biliary complications more than 10 months after transplantation.

Discussion

During the early stages of LDLT development, the biliary system usually was reconstructed by means of a Roux-en-Y hepaticojejunostomy. Later, duct-to-duct reconstruction was introduced, especially for adult LDLT, because of its advantages over hepaticojejunostomy, such as shorter operation time and simpler biliary reconstruction. Furthermore, in the event of leakage at the anastomotic site, serious complications in duct-to-duct reconstructions are rare in contrast to hepaticojejunostomy, where division of the Roux-en-Y limb may be necessary. Therefore, duct-to-duct reconstruction for adult LDLT has been widely accepted in conjunction with the increase in right-lobe LDLT. However,

Table 1. Patient Demographics

Patient	Age/Gender	Disease	Mode of Biliary Reconstruction	Follow-up Periods	Results (Biliary Complication)
1	39/M	HBV	Ant-CD, Post-RHD	13 months	Dead* (none)
2	53/M	HCV/HCC	Ant-RHD, Post-CD	28 months	Alive (none)
3	58/M	HCV/HCC	Ant-CD, Post-RHD	14 months	Alive (none)
4	18/M	Caroli disease	Ant-RHD, Post-CD	13 months	Alive (none)
5	44/F	FHF	Ant-CD, Post-RHD	10 months	Alive (none)

Abbreviations: HBV, hepatitis B; HCV, hepatitis C; HCC, hepatocellular carcinoma; FHF, fulminant hepatic failure; Ant, anterior branch of the right hepatic duct of the graft; Post, posterior branch of the right hepatic duct of the graft; CD, cystic duct of the recipient; RHD, right hepatic duct of the recipient.
*Patient 1 died of chronic rejection.

because there are many variations in bile-duct branches, especially in the case of right-lobe grafts, some modifications are needed for multiple bile-duct reconstructions. Sometimes hepaticojejunostomy combined with duct-to duct reconstruction should be considered for reconstruction of two bile ducts that are too far apart. One of the solutions for this particular problem is to use the cystic duct for one biliary anastomosis. Although use of the cystic duct for duct-to-duct biliary reconstruction has been previously reported, there are few descriptions of this technique as an alternative to a two-bile-duct reconstruction, and none of them report long-term outcomes.[3,9]

Cholangiography performed through the external drainage tubes about one month after transplantation showed no leakage or stricture at the anastomotic site in any of our 5 recipients. During dissection of the bile duct and cystic duct for the recipient operation, we paid attention to preserving the connective tissue around the wall as much as possible to keep the blood supply and tried to ensure the patency of the cystic duct by dilating the spiral lumen before anastomosis. Although Liu et al. reported excellent results for duct-to-duct biliary reconstruction of right-lobe LDLT without biliary drainage[10] and also reported that the biliary stenting was one of the risk factors for biliary complications,[11] we still consider the use of small external drainage tubes preferable because of several advantages. First, it allows us to obtain information about bile juice production and hence about the graft function. Second, biliary drainage can be used to reduce pressure at the anasomotic site to prevent leakage. And finally, the external drainage tubes can help to keep the lumen open, which may be important particularly when dealing with a spiral cystic duct. A recent study described complete obstruction of the anastomosis of a cystic duct and a donor right anterior hepatic duct one month after transplantation because of fibrous tissue replacing the anastomotic site.[12] The

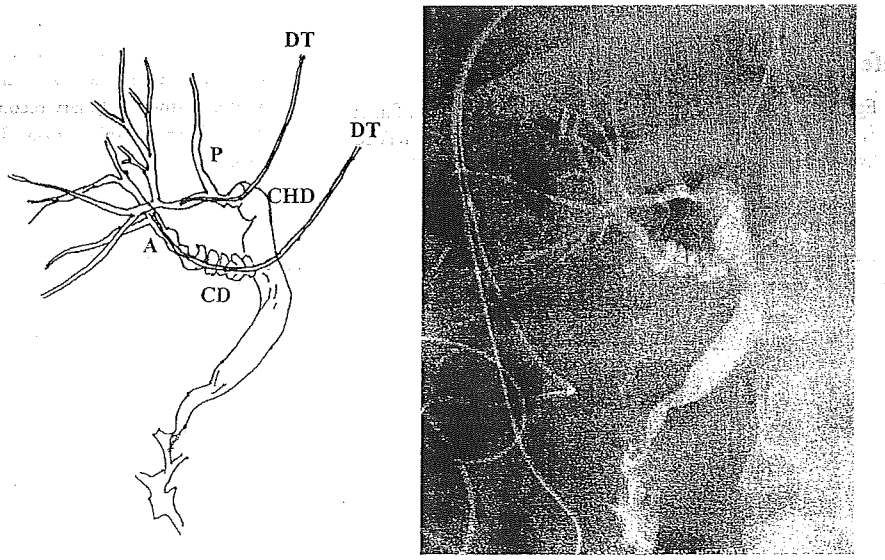

Figure 3. Cholangiography through the external drainage tubes one month after liver transplantation in patient 1. Neither leakage nor stricture was detected. CD, cystic duct; CHD, common hepatic duct; A, anterior branch of right hepatic duct of the graft; P, posterior branch of right hepatic duct of the graft; DT, external drainage tube.

technique described here, including the use of drainage tubes, could avoid early obstruction. In addition, cholangiography can be performed through the tubes to determine whether any leakage or stricture has occurred. However, this technique also has some disadvantages, such as a waiting period of several months before the tubes can be removed because of the possibility of bile leakage from the insertion site in the wall of the bile duct. This is especially problematic when the tubes need to be kept in place for long periods of time, such as in the case of recipients who show continuous ascites after transplantation. Moreover, immediately after we removed the drainage tubes three months post-transplantation, fever, abdominal pain, and signs of infection developed in some recipients and required administration of antibiotics.

These disadvantages are in addition to the fact that biliary strictures occur in 15 to 33% of patients who undergo LDLT with duct-to-duct biliary reconstruction, whereas such strictures do not occur as frequently in hepaticojejunostomy.[2,9,10,13] However, endoscopic access is easier in duct-to-duct reconstruction for either examination or treatment of biliary strictures. Hisatsue et al. reported that 13 of 14 patients who showed biliary stricture after duct-to-duct reconstruction were successfully treated with an internal stent.[14] It could therefore be argued that even though a cystic duct anastomosis has its problems, they are outweighed by the possibility of endoscopic access after transplantation.

In conclusion, using the cystic duct for separated biliary duct reconstruction is a feasible and safe technique as demonstrated by short-term as well as long-term results after LDLT. In addition, external drainage tubes may be effective for preventing leakage or stricture of the cystic duct anastomosis.

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Living Domino Liver Transplantation in an Adult With Congenital Absence of Portal Vein

Takayuki Takeichi, Hideaki Okajima, Hiroko Suda, Shintarou Hayashida, Hironori Iwasaki, Manuel Zeledon Ramirez, Mikako Ueno, Katsuhiro Asonuma, and Yukihiro Inomata

Congenital absence of the portal vein (CAPV) is a rare malformation of the splanchnic venous system. Although CAPV is usually detected in the pediatric age group, our patient was a 35-year-old woman. She had been diagnosed with CAPV in 1996 when she was 27 years old. In 1998, she was placed on hemodialysis due to chronic renal failure. After several episodes of encephalopathy in 2002, liver transplantation (LT) was recommended to her and her family. Since there was no suitable living donor candidate, she was put on the waiting list for a deceased donor liver transplant in Japan. In 2004, her ammonia level increased to around 300 μg/dl, and she went into a coma lasting for three days. After recovering from this event, she underwent a living domino transplantation using a whole liver donated by a familial amyloid polyneuropathy (FAP) patient. Her portal vein, which had drained directly into the inferior vena cava (IVC), was transected together with a cuff of the IVC wall and anastomosed to the graft liver portal vein in an end-to-end fashion. In conclusion, liver transplantation proved to be a safe and effective way to save this patient and improve her quality of life. (*Liver Transpl 2005;11:1285-1288.*)

Congenital absence of the portal vein (CAPV), a rare malformation in which the portal vein does not drain into the liver but into the systemic venous blood vessels, is usually observed in cases of the pediatric age group. In 1793, John Abernethy reported the presence of a porto-caval shunt that completely bypassed the liver in an autopsy of a 10-year-old female,[1] and it was not until 1833 when another case was reported by Kiernan, again detected during autopsy.[2] This long interval indicated a very rare malformation that was noncompatible with adult life.

To date, 47 cases have been reported and 42 of them after 1979. This translates into a rate of almost two cases per year since 1980. In recent years, most of the reported cases have been living patients, mostly pediatric, although the number of adults is increasing. The majority of cases usually show no signs of encephalopathy, even in cases with documented hyperammonemia. Liver transplantation (LT) has rarely been indicated for CAPV, especially for adult cases. To our knowledge, LT has been indicated for portosystemic encephalopathy due to CAPV in only three cases, and two of them were children.[3-5] We herein present an adult patient of CAPV with hyperammonemic encephalopathy who was successfully treated with living domino LT.

Case Report

The patient was a 35-year-old woman without any relevant history of disease during her childhood. Eight years ago, she suffered from an episode of encephalopathy due to hyperammonemia and was referred to our institution. Computed tomography (CT) scan and ultrasonographic examination showed the absence of the portal vein. Because histopathological examination of the liver biopsy showed no portal vein branches within the Glissonean sheath, diagnosis of CAPV was confirmed. Conservative treatment resulted in complete recovery from the encephalopathy, and the patient was discharged from the hospital. Two years later, however, she had to be put on hemodialysis due to chronic renal failure caused by focal segmental glomerulopathy. After the diagnosis of CAPV, her ammonia level gradually increased, and after several episodes of transient hyperammonemia with encephalopathy, LT was recommended to her and her family in 2002. Living donor LT is much more common in Japan than deceased donor LT. However, since there was no suitable living donor available among the patient's relatives, she was put on the waiting list for deceased donor LT, which is

Abbreviations: LDLT, living domino liver transplantation; CAPV, congenital absence of portal vein; LT, liver transplantation; FAP, familial amyloid polyneuropathy; IVC, inferior vena cava.

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Figure 1. Three-dimensional computed tomography (CT) angiography showing the congenital porto-caval shunt (arrow) draining directly to the suprarenal IVC.

associated with limited opportunities in Japan. As expected, after two years on the list, she still had not been allocated a deceased donor liver. Her ammonia level increased to around 300 μg/dl, and she experienced an episode of severe coma lasting for three days. After she had recovered from this event, the possibility of domino transplantation at the chance of an LDLT for a familial amyloid polyneuropathy (FAP) patient was proposed to the patient and the family. After due consideration of the advantages and disadvantages of a domino transplant, they decided to proceed with this procedure.

The preoperative CT scan confirmed the absence of the portal vein and direct drainage of the confluence of the superior mesenteric vein (SMV) and splenic vein into the inferior vena cava (IVC) (Fig. 1). Preoperative laboratory data showed slight liver dysfunction (aspartate aminotransferase [AST], 42 IU/L; alanine aminotransferase [ALT], 43 IU/L), a reduced platelet count ($9.3 \times 10^4/mm^3$), and a severely elevated ammonia level (316 μg/dl).

Laparotomy showed no ascites or any venous collaterals and a spleen of normal size. There was no portal vein in the hepatoduodenal ligament, and the hepatic artery was slightly enlarged. The confluence of the SMV and the splenic vein drained directly into the suprarenal IVC (Fig. 2). A whole liver was donated by a 28-year-old male FAP patient. The graft weighed 1,100 g, and the graft-recipient body weight ratio was 2.4%. After total hepatectomy, the graft liver was implanted orthotopically by means of a piggyback technique.[6] The left and middle hepatic veins of the graft were plastied into one vein on the back table and anastomosed to the recipient's trunk of the middle and left hepatic veins in an end-to-end fashion. The graft's right hepatic vein was anastomosed to the stump of the right hepatic vein. After completion of the hepatic vein reconstruction, the portal vein that had been draining into the IVC was transected together with a cuff of the IVC wall and anastomosed directly to the portal vein of the graft liver in an end-to-end fashion. Total clamping time of the portal vein was only 17 minutes, and there was no intestinal congestion. Arterial reconstruction was per-

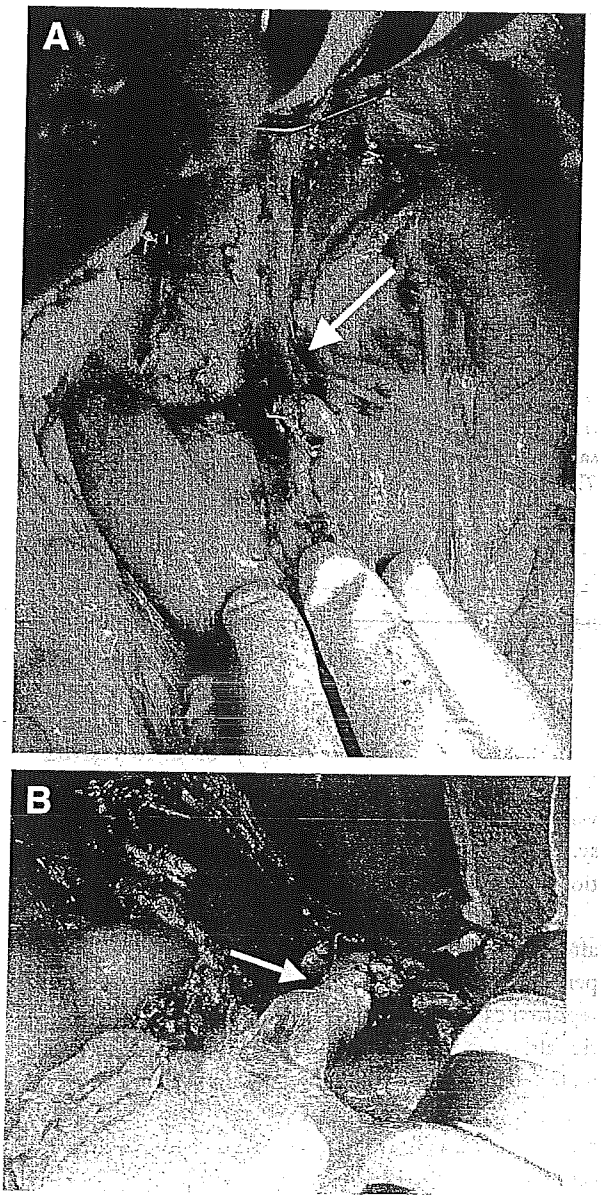

Figure 2. (A) Encircled porto-caval shunt during the transplant operation. (B) Reconstruction of the portal vein. Arrow indicates the anastomosis line.

formed under microscopic observation. The bile duct was reconstructed by a duct-to-duct anastomosis. The postoperative course was uneventful, and the ammonia level immediately dropped to the normal range. Pathological examination of the explanted liver confirmed the diagnosis of CAPV. Three nodules were found in the right lobe, but all were regenerative hyperplasia and not malignant. The patient has been doing well for more than 10 months and enjoying daily activities. She has been followed up by a neurologist in view of the possible occurrence of FAP. Abnormal levels of transthyretin produced by the FAP liver have been detected in her serum since the transplantation, but as of the time of this writing, no neurological symptoms have been detected.

Discussion

CAPV is a rare malformation usually diagnosed during childhood, although several authors have suggested that it might be more common than once thought, and recently the number of cases has been increasing.[4,7] It has been suggested that elevated galactose levels can be used for the early detection of CAPV in newborns,[8] and it has been proposed that early management of CAPV patients could improve their neurological prospects.[9] The absence of the portal venous system is the result of abnormal development during the fourth to 10th weeks of gestation.[10] Morgan and Superina classified portosystemic anomalies into two types based on whether the hepatic parenchyma is perfused with blood from the mesenteric venous system. In type I, the liver is not perfused with portal blood (total shunt; CAPV), whereas in type II, the liver is perfused with portal blood (partial shunt; portal-hepatic venous anastomosis). Type I CAPV is further divided into two subgroups: Ia (SMV and splenic vein do not join to form confluence) and Ib (SMV and splenic vein join to form confluence).[11] Our case was thought to be type Ib. CAPV is often associated with congenital cardiovascular anomalies and/or hepatic tumors,[4] but the majority of CAPV patients usually have normal liver function and no encephalopathy, although they do suffer from hyperammonemia. This explains the scarcity of reports of LT for CAPV.

To the best of our knowledge, LT for CAPV has been indicated in 8 previous cases, only two of whom were adult patients.[5,12] The indication for the transplantation in two of the cases, including ours, was portosystemic encephalopathy, and hematochezia in another case. Portosystemic encephalopathy has not been documented in most CAPV patients, and the reason why it occurs in some adult patients and not in others remains unknown. Wakamato et al. have suggested that the aged brain has a reduced tolerance for ammonia and other metabolities.[9] Nakasaki et al. found that the blood level of ammonia in the superior mesenteric vein was lower than normal in a 14-year-old boy with CAPV, which led them to suggest that this low blood level might indicate the presence of a homeostatic control mechanism.[13] It is of special interest that another LT recipient was on hemodialysis due to chronic renal failure, as was our case. Renal failure may thus contribute to the appearance of portosystemic encephalopathy in adult cases. The combined occurrence of focal segmental glomerulopathy with CAPV should be recorded and analyzed after the accumulation of more cases.

In Japan, organs from deceased donors remain scarce, so the potential liver transplant recipients who do not have a living donor may die while on the waiting list for a cadaveric donor. Therefore, domino LT using a living donor may help to save the lives of a significant number of patients with end-stage liver disease, as it did in our case.[9] By the end of 2003, 25 domino LTs had been registered in Japan, and the number is compatible to that of the total number of deceased donor LTs performed in Japan since the procedure was legalized in 1997. However, the benefit of a minor increase of the donor pool is offset by the fact that recipients of FAP livers have to be carefully observed for the likelihood of amyloid deposition in the future.

In conclusion, severe hepatic encephalopathy associated with CAPV needs LT after the patient reaches adulthood because it is a safe and effective way to save CAPV patients and to improve their quality of life.

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肝移植と胆道閉鎖症

——小児肝移植の現状と，それによる胆道閉鎖症治療体系への影響

Impact of liver transplantation on the strategy of the treatment for biliary atresia

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◎胆道閉鎖症の治療体系は肝移植が一般化するにつれ，葛西手術をまず行い，それによって黄疸消失が得られなかったり，黄疸は消えても肝硬変や種々の合併症をきたす症例に対して，肝移植を行って救命する，というものに変化してきた．葛西手術自体での黄疸消失率は60%程度期待できるようになっているが，黄疸が消失しない症例は1～2歳までに移植が必要となり，黄疸消失例でもその後の肝不全，胆道感染，肝肺症候群などで成人に至るまでの種々の年齢で移植が実施されることがあり，すくなくとも胆道閉鎖症全体の半数程度は肝移植を必要としている．胆道閉鎖症肝移植後1年生存率は85%以上あり，成人肝硬変より良好である．肝移植の広がりとともに，葛西手術後に予測される肝移植での弊害を想定して葛西手術での胆道再建術式の単純化，再手術適応症例の限定，遅い診断例での葛西手術をスキップした一次的肝移植適応の考慮，などの変化がみられる．

Key word：胆道閉鎖症，肝移植，生体肝移植，葛西手術

胆道閉鎖症に対する肝移植の現状

胆道閉鎖症の根治術として日本から葛西手術が開発紹介されたのは世界でも肝移植が展開される前の1950年代であるが，欧米では葛西手術の治療効果が評価される前に肝移植医療が広く行われるようになり，一時は胆道閉鎖症治療の第一選択肢は肝移植と考えられる時期があった．これと逆に日本では移植医療が進まない一方で葛西手術の評価認知が確立しその手術管理についての議論が尽くされて術後成績は向上していった．しかし，葛西手術後にも肝不全がすべては予防できず，脳死移植がまったく不可能であることを背景に，葛西術後の胆道閉鎖症患児を対象に，1989年，島根医大で日本初の生体肝移植が施行され，日本の生体肝移植時代が幕を開けた．日本肝移植研究会の登録では1989～2003年までで，成人症例1,355例に対し18歳未満の小児肝移植は通算1,260例実施され，このうち，1,001例80%が胆汁うっ滞性疾患で占められ，さらに，925例73%は胆道閉鎖症である(図1)[1]．同一期間の，胆道閉鎖症研究会による症例集計数は1,804名である．肝移植研究会の集計対象には1989年以前の胆道閉鎖症症例も当然含まれるので，同一対象となっていないが，ラフに計算すると，約半数の胆道閉鎖症が種々の時期に移植を受けてきたこととなる．胆道閉鎖症研究会の2002年の集計によると，2002年までの登録症例全体では28%が移植を受けているが，年度別では1994年登録症例中30%に対し2000年登録症例108例中では45例，42%が調査時点で移植を受けている[2]．最近の肝移植研究会の移植症例登録集計との差をみると，葛西手術実施施設とその後の肝移植実施施設のいずれからも胆道閉鎖症研究会への移植実施報告が行われていない症例があると思われ，胆道閉鎖症で肝移植を受けている

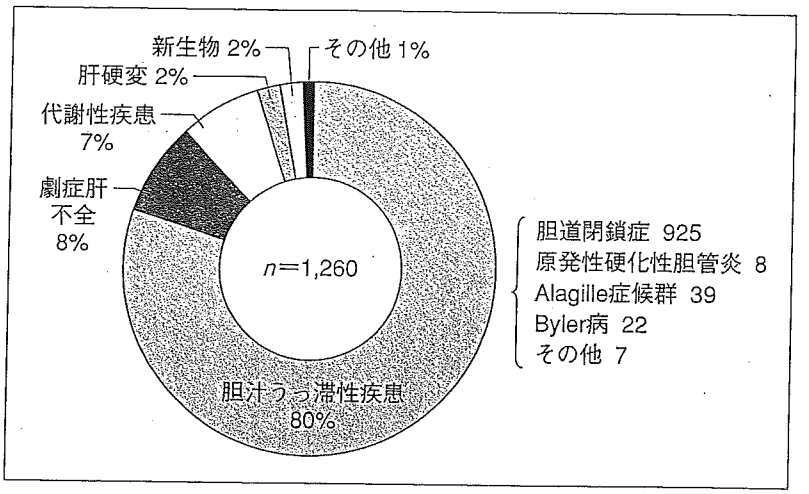

図 1　わが国の小児肝移植適応疾患(～2003.12 日本肝移植研究会 18 歳未満)

症例の割合は肝道閉鎖症研究会の集計より多いと思われる.登録開始から 2003 年までの胆道閉鎖症死亡症例は 146 名で, 1995 年以降集計の肝移植後死亡 44 例が含まれるので,多く見積もって 780 名ほど(全症例の約 43%程度)が移植を受けずに生存しているものと推測される.

1999 年以降, 日本でも脳死肝移植が実施されているが, 胆道閉鎖症に対する脳死肝移植実施数は 2003 年までで 8 例にすぎず, ほとんどが生体肝移植である. 年間の全国小児生体肝移植症例数は 2000 年以降はほぼ 150 例程度で安定しており, 胆道閉鎖症の発症数を勘案するとほぼこれで小児肝移植の需要を満たしているものと推測される[1].

胆道閉鎖症の治療の変遷
――なにが変わり, なにが変わっていないか
1. 肝移植の成績の変化

肝移植の治療成績が国内でもしだいに評価できるものになってきたことが胆道閉鎖症の治療体系変遷のもとになっている. 胆道閉鎖症に対する生体肝移植は 1998 年以降健康保険適応となり, 経済的負担の軽減は移植症例の増加やその実施年齢の変化に影響を与えたと考えられる.

京大病院における時期別の生体肝移植 1 年生存率の変化をみると, 症例が増加して一定した 1995 年ごろに比べると最近は 5～10%の改善がみられる(図 2). 緊急症例や高度に悪化した肝不全患者の減少は成績向上に寄与する要因となる. もちろん, 免疫抑制状態維持に関するノウハウの蓄積は大きく, 必要とされる免疫抑制レベルはしだいに低くなり, EB などウイルス感染症に対する予防策も充実してきたことも小児肝移植成績向上に寄与していると考えられる. 移植時年齢は, 症例数の多い京都大学の胆道閉鎖症に対する初回移植例集計でみると, 乳児期が約 1/3 を占め, 1 歳がそれに続いている. 以後各年齢に分散するが, 20～30 歳代という成人例も少なくない. 年長児以降の移植適応は, 腹水, 消化管出血などの肝不全兆候のほか, 胆管炎など感染, 肝肺症候群(「サイドメモ 1」参照)などからの生命リスクや生活の質の低下が主である. 京都大学での最若胆道閉鎖症レシピエントは, 生後 4 月, 最少体重レシピエントは 4.2 kg であり, 一方, 最年長は 34 歳であった. 胆道閉鎖症のグラフトは, 多くが左外側区域, あるいは左葉であるが, 小さい乳児には外側区域よりさらに小さい単区域移植が行われ, 体重を気にして時期を逸するということは, すくなくとも胆道閉鎖症ではほとんどなくなったといってよい[3]. また, 成人例では右葉が移植されることも増加している. 葛西手術なしのいわゆる一次的肝移植は, 診断が遅れた症例に対して行われており, 胆道閉鎖症研究会のまとめでは 1989 年からの集計 1,804 名のうちわずか 5 例(0.27%)であり, 現在の日本の大多数の胆道閉鎖症肝移植は葛西手術後に行われている[3]. 胆道閉鎖症に対する肝移植の成績は時期や施設によって差があるが, 肝移植研究会

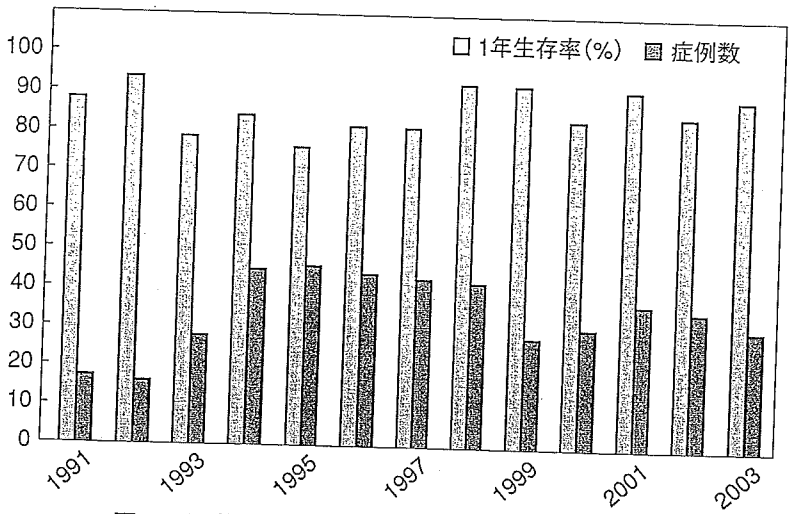

図 2　胆道閉鎖症移植時期別1年生存率(京大病院)

の集計では5年生存率で85.9%，10年生存率で80.4%と，1年以降の生存率はそれほど時間経過によって低下しない傾向にあり，他の疾患に比べてもよい傾向にある(表1)[1]．ただ，移植年齢と移植後生存率に関係があることも判明しており，脳死肝移植中心の欧米では乳児期のほうが不良であるのに対し国内の生体肝移植では年長時期の移植予後のほうが不良の印象がある[4,5]．その理由は容易に説明できないが，癒着の程度や側副血行の発達，部分生体肝移植に頼る日本での成人症例での相対的過小グラフトの問題などが絡んでいるものと推測される．

血液型不適合移植も小児では比較的以前から行われてきたが，乳児期の移植症例がさほど影響を受けない傾向は変化ないが，免疫抑制の工夫により年長児，成人症例もやや成績が改善しつつある[1]．

移植後長期成績としては，成長発育の問題と，免疫反応，移植免疫寛容の問題がある．成長発育に関しては術前肝不全による遅延が移植後著明に改善することが知られてきたが，思春期以降に移植を受けた症例での改善不良も指摘されており，移植時期決定に影響を与えている[6]．胆道閉鎖症肝移植後免疫に関して最近の大きな関心事は移植後数年での自己免疫性肝炎発症が最近内外で報告されていることである[7]．自己抗体の測定や，ステロイド投与の検討が必要になってきている．一方，免疫抑制離脱，寛容導入の考え方も小児肝移植で大きなトピックであり，実際に生体肝移植後寛容

表 1　肝移植後生存率(日本肝移植研究会 1989～2003)

	症例数	累積生存率(%)			
		1年	3年	5年	10年
成人(18歳以上)	1,365	76.9	72.7	70.3	69.5
小児	1,302	85.5	83.8	82.5	77.5
胆道閉鎖症	992	88.1	87.1	85.9	80.4

へ至った小児症例は多く，今後，どのような症例でこれが可能か，の推定指標が検討されている．

2. 葛西手術の変化
——胆道再建法の変化，再手術と移植の関係

肝移植導入後のわが国でも胆道閉鎖症治療に対する第一選択としての葛西手術の意義は不変である．1980年代アメリカでの，肝移植を第一義に考

サイドメモ1　肝肺症候群

基礎疾患のいかんにかかわらず，肝硬変に門脈大循環系のシャントを伴う場合，本来肝で代謝されるべき血管拡張物質(種々のものが想定されているが，サブスタンスP，VIPなど)が代謝されずに肺の微小血管に作用し，肺動静脈の末梢レベルでのシャントを生じ，低酸素血症となる．胆道閉鎖症でも年長児以降にみられることがあり，黄疸がない症例での移植適応の1因となっている．心内シャントを否定したうえで，コントラスト心エコー検査，マイクロアルブミンを用いた肺血流シンチグラムなどで診断される．肝移植によって可逆的であるが，重度の低酸素血症をきたしている状態では移植手術自体の合併症率が高くなる．