Hiroshima J. Med. Sci.
Vol. 47, No.1, 31~37, March, 1998
HIJM 47-5

Living Related Partial Liver Transplantation for Primary Biliary Cirrhosis – A case report

Toshimasa ASAHARA[1], Kiyohiko DOHI[1], Keiso SUGINO[1], Seiji MARUBAYASHI[1], Hideki OHDAN[1], Toshio NORIYUKI[1], Kouji KATAYAMA[1], Toshiyuki ITAMOTO[1], Toshio NAKANISHI[2], Susumu TAZUMA[2], Goro KAJIYAMA[2], Katsufumi MORIWAKI[3], Osafumi YUGE[3], Minako OTANI[4], Seiji OKABAYASHI[4], Takashi YOKOYAMA[5], Fumio SHIMAMOTO[6], Hisao ITOH[7] and Tatsushi YOKOYAMA[8]

1) 2nd Department of Surgery, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan
2) 1st Department of Internal Medicine Hiroshima University School of Medicine
3) Department of Anesthesiology and Critical Care Medicine, Hiroshima University School of Medicine
4) Division of Emergency and Critical Care Medicine, Hiroshima University School of Medicine
5) Department of General Medicine, Hiroshima University School of Medicine
6) Department of Pathology, Hiroshima University Hospital
7) 1st Department of Pathology, Tottori University School of Medicine
8) Department of Internal Medicine, Hiroshima General Hospital of the West Japan Railway Company

ABSTRACT

An adult living related partial liver transplantation was performed on a 49 year old female with terminal hepatic failure due to primary biliary cirrhosis (PBC). The donor was her 53 year-old sister. A sufficient volume of graft tissue was obtained, which comprised 1.5 % of the body weight of the recipient. The recipient had an excellent recovery without any major complications, and was discharged 35 days after the operation. At 15 months after the operation, the patient has shown no signs of rejection while using FK506 and prednisolone as immunosuppressants. The progression of symptomatic PBC can be predicted, and the timing of the transplantation can be easily determined. In addition, the results of liver transplantation for PBC are good. Therefore, adult living related partial liver transplantation is an excellent treatment for primary biliary cirrhosis.

Key words: *Liver transplantation, Biliary cirrhosis, Living related partial liver transplantation*

Liver transplantation is a good indication for the treatment of primary biliary cirrhosis. This study reports the case of a 49-year-old woman with hepatic failure due to advanced primary biliary cirrhosis. She was treated with a living related partial liver transplantation; the donor was her older sister. The indication for this treatment and several points to be taken in account are also discussed.

CASE REPORT

Patient: a 49-year-old female
Chief complaint: general fatigue
Past history: appendectomy at 18 years old
Family history: unremarkable

Present illness: In January 1990, she began to experience general itchiness of the whole body. In February 1991, jaundice was diagnosed by her family doctor, who then referred her to the Department of Internal Medicine of the Hiroshima General Hospital of the West Japan Railway Company. Hematological and biochemical studies revealed elevated biliary enzymes, the presence of anti-mitochondrial antibody (AMA) elevated more than 320-fold, and a high IgM titer. The results of a liver biopsy confirmed that her disease was primary biliary cirrhosis (PBC). Initially, she was treated with medication including steroids. However, the prolonged use of steroids and other drugs induced glucose intolerance, osteoporosis and drug-induced biliary congestion. Gradually, her illness progressed with exacerbating jaundice and the development of ascites. At this point, she was transferred to our department to be treated with a liver transplantation.

Data from her physical examination and laboratory tests on admission were as follows: height 141 cm and weight 49 kg. The jaundice was severe and abdominal distension was observed. The liver was palpable at a three finger breadth beyond the costal margin.

A hematological study indicated anemia; her laboratory values were as follows: RBC 276 × 10^4/mm^3, Hb 5.8g/dl, Hct 17.6%, platelets 30 × 10^4/mm^3. Biochemical tests also indicated liver function abnormalities (Table 1) such as total bilirubin 20.6mg/dl, direct bilirubin 14.8mg/dl,

Table 1. Laboratory data of the recipient on admission

WBC (/mm³)	7000	T-Bil (mg/dl)	20.6
RBC (×10⁴/mm³)	276	D-Bil (mg/dl)	14.8
Hb (g/dl)	5.9	AST (U/liter)	63
Ht (%)	17.6	ALT (U/liter)	22
Platelet (×10⁴/mm³)	30.0	LDH (U/liter)	585
		Ch-E (U/liter)	109
PT (%)	31	ALP (U/liter)	1275
ATPP (sec)	183.8	LAP (U/liter)	96
AT III (%)	51	γ GTP (U/liter)	48
HPT (%)	64.9	TP (g/dl)	5.5
		Alb (g/dl)	2.5
NH_3 (μg/dl)	57	T-Chol (mg/dl)	134
		BUN (g/dl)	13
CMV IgG (UA/ml)	120	Creatinin (g/dl)	0.47
CMV antigenemia	(–)	Na (mEp/liter)	142
HSV	×8	K (mEp/liter)	3.5
VZL	×4	Cl (mEp/liter)	111
EBV VCA IgG	×40		
HTLV Ab	(–)	HBs Ag	(–)
CD3	76.7	HBs Ab	(–)
CD4	45.5	HBs Ab	(–)
CD8	19.9		
CD4/CD8	2.29	anti-mitochondrial Ab	×80
		anti-mitochondrial Ab	×265

Table 2. HLA typing of the sisters

locus	A	B	C	BW 4/6	DR
recipient	24	51	W1	4	15
	11	52	W5		12
donor	24	51	W1	4	15
	11				12

ALPH 1275IU/liter, total protein 5.5g/dl, albumin 2.5g/dl, Cho-E 109IU/liter, total cholesterol 134IU/liter, PT 31%, APTT 138.8 sec, ATIII 51% and HPT 64.9%. The diagnostic markers for PBC were also abnormal, with the anti-mitochondrial antibody (AMA) titer at × 80 and AMA M2 at × 265.

Table 2 shows the HLA typing of the sisters, which was a complete match (Table 2).

Gastrointestinal fiberscopy identified esophageal varices classified as F2, Cw, Lm, RC (++) and Lg (–). The volume of the liver of the recipient was inferred from a preoperative CT scan at 1468 ml (Fig. 1). The mortality prediction by a logistic recurrent model was 89.9% at a point in time six months later. These data therefore validated the liver transplantation surgery.

Donor: 53-year-old female (sister)

Past history: unremarkable

Family history: unremarkable

Data from physical examination and laboratory tests on admission: height 160 cm and weight 83 kg. No other abnormality was observed other than obesity. Her blood type was B, the same as the recipient. HBsAg (–), HCV Ab (–) and other viruses were also negative, except for EBV VCA IgG (FA) (160) and CMV IgG (×72). No antigenemia was detected for either of the two viruses. The hematological and biochemical studies were normal, and AMA and AMA M2 were negative (Table 3).

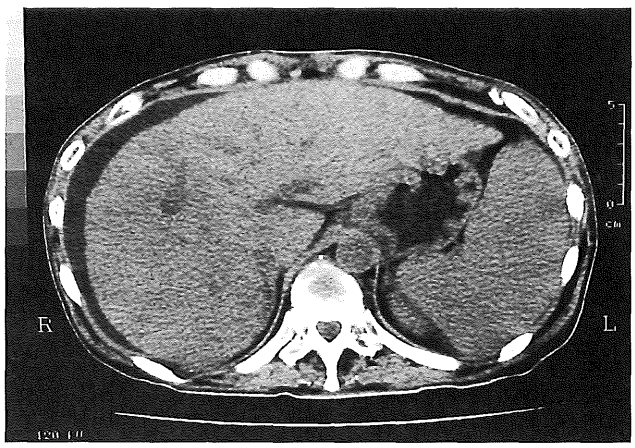

Fig. 1. Preoperative CT scan of the recipient

Digital subtractive angiography before the operation revealed that the left hepatic artery and the middle hepatic artery formed a common trunk (Fig.2). Volumetry of the liver before the operation indicated that the volume of the left lobe was 588.8 ml (Fig. 2). The percentage of the weight of the left lobe to the whole body was 1.2%. No abnormalities of the intrahepatic vessels or parenchyma were found on an echogram. To

Table 3. Laboratory data of the donor on admission

WBC (/mm³)	4900	T-Bil (mg/dl)	0.6
RBC (× 10⁴/mm³)	475	D-Bil (mg/dl)	0.1
Hb (g/dl)	13.9	AST (U/liter)	14
Ht (%)	40.2	ALT (U/liter)	15
Platelet (×10⁴/mm³)	21.9	LDH (U/liter)	359
		Ch-E (U/liter)	428
PT (%)	81	ALP (U/liter)	268
ATPP (sec)	29.6	LAP (U/liter)	42
AT III (%)	95	γ GTP (U/liter)	18
HPT (%)	102	TP (g/dl)	7.1
		Alb (g/dl)	3.8
CMV IgG (UA/ml)	72	T-Chol (mg/dl)	190
CMV antigenemia	(–)	BUN (g/dl)	16
HSV	×8	Creatinin (g/dl)	0.57
VZL	×4	Na (mEp/liter)	142
EBV VCA IgG	×160	K (mEp/liter)	4.2
HTLV Ab	(–)	Cl (mEp/liter)	106
		HBs Ag	(–)
		HBs Ab	(–)
		HCV Ab	(–)
		anti-mitochondrial Ab	< ×10
		anti-mitochondrial Ab (M2)	< ×4

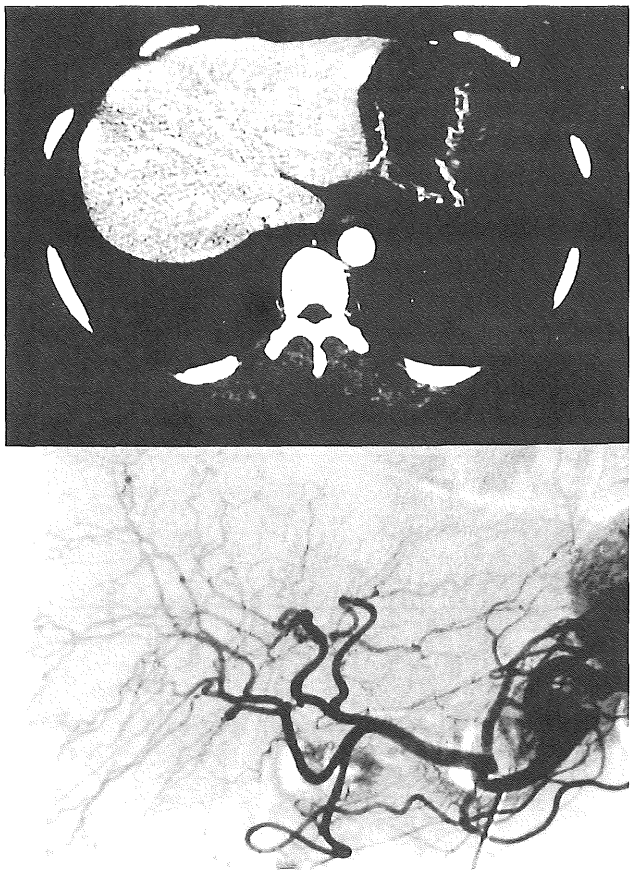

Fig. 2. Preoperative CT scan and hepatic arteriogram of the donor

improve the general condition of the recipient, plasma exchange was performed with 3 liters of fresh frozen plasma on July 11. On July 16, 1996, the living related partial liver transplantation was performed. The left lobe of the donor liver was resected at the right of the middle hepatic vein. The removed left lobe was grafted orthotopically into the recipient, whose whole liver had been excised. For the donor, the operation time was 7 hr 40 min, the bleeding was 1400 ml, and the excised left lobe was 716 g, comprising 1.5 % of the whole body weight of the recipient. For the recipient, the operation time was 12 hr 43 min with 2000 ml of bleeding. The weight of the excised liver was 1357g. The liver transplantation procedure for the recipient was as follows. After the excision of the sick liver as a whole, the right hepatic vein of the recipient and the left hepatic vein of the graft were anastomosed end-to-end, and then the portal vein of the recipient and the left portal vein of the graft were anastomosed end-to-end, thus resuming circulation of the graft. The hepatic artery of the recipient and the left hepatic artery of the graft were anastomosed end-to-end using microvascular techniques. Finally, reconstruction of the bile duct was performed by the Roux-Y method (Fig. 3). Fig. 4 shows the change of the oxygenation status of hemoglobin (HbSa (%): oxygen saturation of hemoglobin in the graft) during the operation from laparotomy of the donor, recirculation of the portal vein, and the resumption of the flow of the hepatic artery

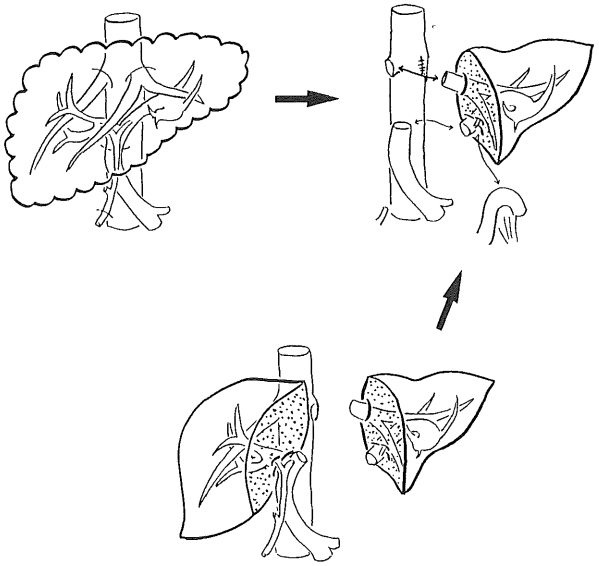

Fig. 3. Operative procedure of living related partial liver transplantation

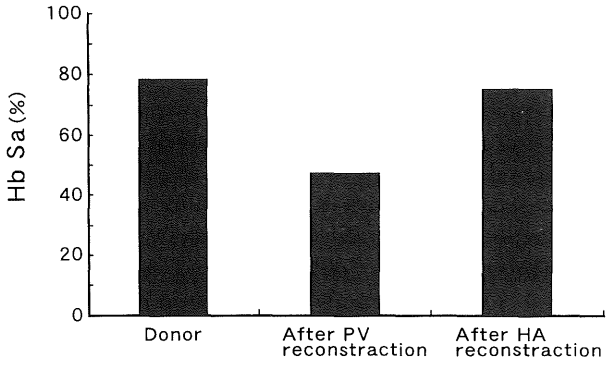

Fig. 4. Hb saturation in graft liver tissue measured by NIR spectroscopy

(Fig.4). The oxygen saturation of the graft was determined with the near infrared light spectroscopy method. The amount of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) was measured by subtracting the near infrared spectrum of the non-circulating graft where no hemoglobin was present from that of the circulating graft at each time point. The HbSa was calculated as follows:

HbSa = oxy-Hb / oxy-Hb + deoxy-Hb

As shown in Fig. 4, the HbSa at the time of the laparotomy of the donor was approximately 80 %. The HbSa at the recirculariza tion of the portal vein and hepatic artery was approximately 48 % and 80 %, respectively. This means that the circulation of the graft recovered completely to a level similar to at the time of the laparotomy of the donor.

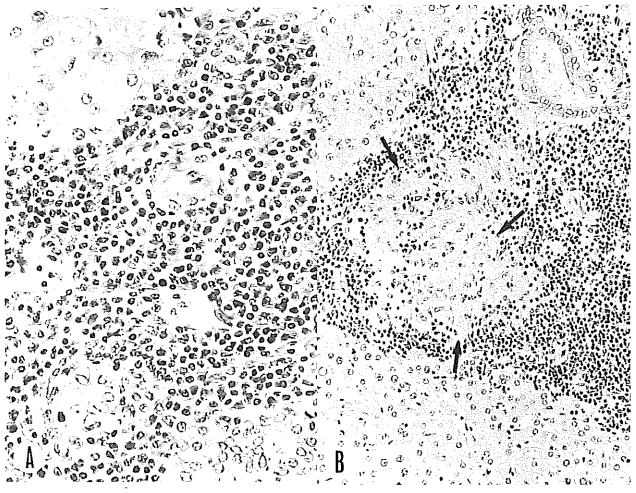

Fig. 5. Histological findings of the donor's caudate lobe which was resected at graft harvesting

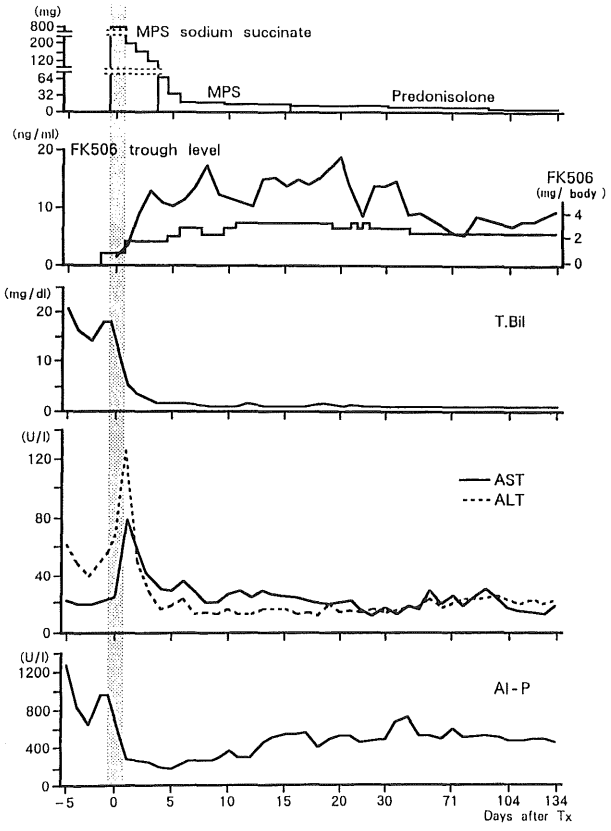

Fig. 6. Course of the recipient after liver transplantation

Fig.5 shows the histological picture of the caudate lobe resected from the donor at graft harvesting. This picture shows the infiltrating lymphocytes around the portal veins and the formation of the granulation. These were found only in the noted area but suggested the early stage of PBC. Then

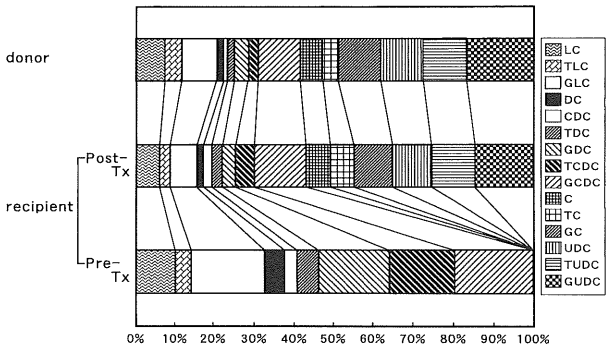

Fig. 7. Fraction of bile acids before and after the transplantation

the donor was diagnosed as asymptomatic of PBC.

Fig. 6 shows the course of the recipient after the transplantation. Transient somnolence and confusion were observed, which disappeared by five days after the operation. The total bilirubin concentration promptly declined to a normal level of 1.1 mg/dl by ten days after the operation. Immunosuppression was provided by prednisolone and FK506, and no signs of rejection were noted during hospitalization. The trough level of FK506 was stable. Fig.7 shows the fraction of bile acids before and after the transplantation, for both the donor and the recipient. The pattern of the bile acid fraction of the recipient after the operation differed from her preoperative pattern, and was identical to the donor pattern. Glucose intolerance developed, presumably as a complication of prednisolone, and was treated with insulin. The recipient was discharged 35 days after the operation. At the present time point of 15 months after the operation, immunosuppressants FK506 (2.5 mg/day) and prednisolone (5 mg/day) are being administered orally and observation is continuing at the outpatient clinic. No complications including rejection have been observed thus far.

DISCUSSION

PBC often occurs in females after middle age, with symptoms such as itchy skin, jaundice and portal hypertension. However, some patients are asymptomatic. The criteria for its diagnosis are indicated in the report published in 1992 by The Incurable Hepatitis Study Group of the Welfare Ministry of Japan. It described a familial predisposition, and suggested the contribution of genetic factors. Immunological factors have also been documented, including a correlation with DR8 antigen of the MHC class II[8,10,11] and C4AQ0 of MHC class III[11].

The treatment for PBC consists primarily of symptomatic treatments against (a) progressive biliary congestion, (b) progressive liver damage, (c) portal hypertension, especially esophageal varices, and (d) extrahepatic complications such as bone lesions and skin itchiness. Although the prognosis of asymptomatic patients is good, the outcome for symptomatic patients with a progressive disease is poor, in spite of many recent trials using ursodeoxycholic acid (UDCA) and several immunosuppressants (prednisolone, azathiopurine, cyclosporin etc.).

Patients with advanced PBC are good candidates for liver transplantation. Symptomatic PBC always exhibits progressive biliary congestion, resulting in terminal hepatic failure. The progression is relatively slow, and can be predicted by several methods such as the Mayo model[5] and European model[3], which help surgeons determine the timing of the transplantation. According to a nation-wide study in Japan, the critical prognostic factors are the patient's age and the serum concentrations of total bilirubin and albumin[9]. The 5-year survival of PBC patients who had undergone transplantation was 70 %, which is clearly higher than the 10% in non-transplanted patients[12]. Therefore, liver transplantation has been applied extensively in Europe and North America. Weisner and colleagues[17] reported a clear correlation between the risk score and the medical costs during the six months after the operation, and suggested that the transplantation should be performed before the development of a serious condition. Neuberger and colleagues[13] examined the relationship between the serum bilirubin concentration and the one-year survival rate, and concluded that patients should be transferred to a transplantation center before the total bilirubin levels reached 8.8 mg/dl (150 μmol/liter). Benhamou and colleagues[2] also suggested that the serum bilirubin concentration was a good indicator of when the transplantation should be done. Generally, a transplantation is indicated when the total bilirubin concentration reaches approximately 8 mg/ml. In the case reported here, the total bilirubin concentration immediately before the operation was 20.6 mg/dl. This indicates that the patient was at a rather late stage for the transplantation.

Liver transplantation for PBC has resulted in a good outcome, because (a) the natural course of the disease is well studied, (b) the patients are relatively young, and (c) the other organs are rarely complicated. According to a report by the UNOS in 1995[11], PBC was at the top of the list of liver diseases with biliary congestion which were treated by liver transplantation. A total of 1558 operations had been performed by 1994, with 239 cases in 1994 alone. The number is now on the rise. The results of a liver transplantation for PBC are better than for other liver diseases; survival rate at one, three, five and seven years after the operation was 85%, 81%, 79% and 71%, respectively.

One problem for liver transplantation for PBC is the recurrence of the disease in the graft. Although the Pittsburgh group did not observe recurrence in the grafts[4,7], other groups have. For example, Polson and colleagues[14] reported recurrence after transplantation in 9 out of 19 cases (47%), Balan and coworkers[1] in 5 out of 60 cases (8%), and Dmitrewski and colleagues[6] in 7 out of 27 cases (26%). Controversy over the recurrence of PBC and differences in its frequency can be attributed to difficulties in differentiating recurrence from rejection. One landmark of recurrence is the presence of florid duct lesions, whereas vanishing bile duct syndrome (VBDS) is a characteristic lesion seen in rejection. These are sometimes indistinguishable, because both lesions occur in the same bile duct epithelium. Biliary lesions due to infection and drug reaction are also sometimes hard to discriminate from recurrence or rejection. The important findings useful for the discrimination of VBDS and PBC, however, are that VBDS shows a relatively mild infiltration of lymphocytes and plasma cells, as well as narrowing or occlusion of the artery in the portal area.

In this study, the function of the graft from the living donor before and after the transplantation was monitored using the near infrared light spectroscopy method, and was found to be favorable. Although this method is applicable to diagnosis of primary graft nonfunction, we are extending its application further to the diagnosis of early rejection using animal models. We are also exploring the possibility of early detection of rejection by continuous measurement of the biliary acid fraction in the serum.

In Japan, living related partial liver transplantation has been performed mainly for children with congenital biliary atresia (CBA) in about 430 patients at Kyoto University, Shinshu University, Tokyo Women's Medical College and others as of December 1996. On the other hand, adult cases of liver transplantation consisted of only about 40 cases as of December 1996, and comprise no more than 9% of the total number of liver transplantations performed in Japan. Liver transplantations are skewed towards children because (a) organ donation from brain-dead donors is not allowed in Japan, (b) it is difficult to obtain a sufficient volume of liver tissue for the adult recipient from a donor, and (c) liver grafts for children are easily obtained from their parents. In the case reported here, the graft was obtained from the patient's older sister. A sufficient volume of graft tissue (716g; 53% of the recipient's liver weight of 1357g; 1.5% of the whole body weight of the recipient), was obtained due to the good body physique of the donor, thus leading to the success of the operation.

Although living related partial liver transplantation has the drawback of damaging healthy donors, it will persist until organ donation from brain-dead donors is permitted. Even when liver transplantation from brain-dead donors becomes possible, living related transplantation will persist as a last resort because of the anticipated shortage of donors. To make adult living related partial liver transplantation safer, advanced methods such as the auxiliary partial orthotopic liver transplantation (APOLT) method being tested in Kyoto University must be developed. According to Tanigawa's survey[16], the overwhelming majority of patients waiting for liver transplantation in Japan are adult patients. The annual number of patients with PBC who require liver transplantation is about 100 cases a year. However, only 9 cases of PBC have been treated with liver transplantation thus far, although results of the liver transplantation are better for PBC patients than for other disorders of the liver. We recommend that living related partial liver transplantations be performed more extensively for patients with PBC, although the number of transplants will not increase dramatically due to the fact that a sufficient volume of the graft must be taken from healthy donors for adult patients.

ACKNOWLEDGEMENTS

We would like to express our great gratitude to all of the stuff at Hiroshima University Hospital who helped us finish this work. In particular, we would like to thank the members of the Pharmaceutical Department who contributed to the measurement of the blood concentration of FK506 and preparation of the drugs, the members of the Department of Blood Transfusion who performed the cross matching tests and plasma exchange, the stuff of the Central Laboratory who willingly accepted our emergency requests, the stuff of the Department of Orthopedics who gave us advice about the diagnosis and treatment of the bone lesions, the stuff of the Third Department of Internal Medicine who gave us advice about the examination and treatment of the neurological complications, the nursing stuff at the East 2 ward, the Intensive Care Unit, the West 1 ward and the Operation Unit, and the office clerks of our hospital.

(Received October 14, 1997)
(Accepted February 27, 1998)

REFERENCES

1. **Balan, V., Batts, K.P., Polayko, M.K., Krom, R.A.F., Ludwig, J. and Weisner, R.H.** 1993. Histological evidence for recurrence of primary biliary cirrhosis after liver trasnplantation. Hepatology **18:** 1392–1398.
2. **Benhamou, J.P.** 1994. Indication for liver transplantation in primary biliary cirrhosis. Hepatology **20:** 11S–13S.

3. **Christensen, E., Neuberger, J., Crowe, J., Altman, D.G., Popper, H., Portmann, B., Doniach, D., Ranek, L., Tygetrup, N. and Williams, R.** 1985. Beneficial effect of azathioprine and prediction of primary biliary cirrhosis; final results of an international trial. Gastroenterology **89:** 1084–1091.
4. **Demertis, A.J.** 1988. Pathologic analysis of liver transplantation for primary biliary cirrhosis. Hepatology **8:** 939–947.
5. **Dickson, E.R., Grambsch, P.M., Fleming, T.R., Fisher, L.D. and Langworthy, A.** 1989. Prognosis in primary biliary cirrhosis; model for decision making. Hepatology **25:** F119–126.
6. **Dmitrewski, J., Hubscher, S.G., Mayer, A.D. and Neuberger, J.M.** 1996. Recurrence of primary biliary cirrhosis in the liver allograft; the effect of immunosuppression. J. Hepatol. **24:** 253-257.
7. **Esquival, C.O., van Thiel, D., Demetris, A.J., Bernardos, A., Iwatsuki, S., Markus, B.H., Gordon, R.D., Marsh, J.W., Makowka, L., Tzakis, A.G., Todo, S., Gavaler, J.S. and Starzl, T.E.** 1988. Transplantation for primary biliary cirrhosis. Gastroenterology **94:** 1207– 1216.
8. **Gores, G.J., More, B., Fisher, L.D., Powell, F.C. and Dickson, E.R.** 1987. Primary biliary cirrhosis; Associations with class II major histocompatibility complex antigens. Hepatology **7:** 889–892.
9. **Inoue, K.** 1994. Primary biliary cirrhosis, 13th Nation-wide Study. 1992, p.76-80, Report of Incurable Hepatitis Study Group of the Welfare Ministry of Japan. Welfare Ministry, Tokyo.
10. **Maeda,T., Onishi, S., Saibara, T., Iwasaki, S. and Yamamoto, Y.** 1992. HLA DRw8 and primary biliary cirrhosis. Gastroenterology **103:** 1118–1119.
11. **Manns, M.P., Bremm, A., Schneider, P.M., Notghi, A., Gerken, G., Prager-Eberie, M., Stradmenn-Bellinghausen, B., Meyer, K.H. and Rittner, C.** 1991. HLA DRw8 and component C4 deficiency as risk factors in primary biliary cirrhosis. Gastroenterology **101:** 1367–1373.
12. **Markus, B.H., Dickson, E.R., Grambsch, P.M., Fleming, T.R., Mazzaferro, V., Klintmalm, G.G., Weisner, R.H., van Thiel, D.H. and Starzl, T.E.** 1989. Efficacy of liver transplantation in patients with primary biliary cirrhosis. N. Engl. J. Med. **320:** 1709–1713.
13. **Neuberger, J.M., Gunson, B.K., Buckels, J.A.C., Elias, E. and McMaster, P.** 1990. Referral of patients with primary biliary cirrhosis for liver transplantation. Gut **31:** 1069–1072.
14. **Polson, R.J., Portmann, B., Neuberger, J., Calne, R.Y. and Williams, R.** 1989. Evidence of disease recurrence after liver transplantation for primary biliary cirhosis. Gastroenterology **97:** 715–725.
15. **Steven, H.B., Kimberly, C.B. and Katherrine, M.D.** 1996. An update on liver transplant in the United States: Recipient characteristics and outcome, p.19-33. *In* J. M. Cecka and P.I. Terasaki (eds.), Clinical transplants 1995, UCLA Tissue Typing Laboratory, Los Angeles.
16. **Tanigawa, K., Yamanaka, M., Teraoka, T., Makuuchi, M., Takagi, H., Monden, M. and Shiraki, K.** 1993. Study for the indication and systems of liver transplantation. 1993. pp.106–113, Report-Clinical Research for Organ Technology of the Welfare Ministry of Japan, Welfare Ministry, Tokyo.
17. **Weisner, R. H., Porayko, M., Dickson, E. R., Gores, G. J., LaRusso, N. F., Hay, J. E., Wahlstrom, H. E. and Krom, R. A. F.** 1992. Selection and timing of liver transplantation in primary biliary cirrhosis and primary sclerosing cholangitis. Hepatology **16:** 1290–1299.