First Successful Application of Side-to-Side Intrahepatic Cholangiojejunostomy to Biliary Obstruction after Living-Donor Liver Transplantation

Biliary anastomotic stenosis has been the most intractable problem after living-donor liver transplantation (LDLT) (*1, 2*). We first applied the side-to-side intrahepatic cholangiojejunostomy to biliary obstruction after LDLT. We here report our surgical techniques and the successful outcome of the procedure after 34 months.

A 49-year-old woman was diagnosed with primary biliary cirrhosis 15 years ago. She developed liver failure with gastrointestinal bleeding caused by esophageal varices and subsequently underwent LDLT. The donor was the patient's brother. The left lobe of the liver was harvested. Biliary reconstruction included a duct-to-duct anastomosis between the left hepatic duct of the donor and the common hepatic duct of the recipient. After anastomosis, a 5 F stenting tube was inserted toward the graft hepatic duct from the stump of the cystic duct. LDLT was successfully completed, and the patient postoperatively recovered without biliary complications.

However, 3 months later, the patient occasionally experienced delayed bile leakage when the stenting tube was removed. Immediately, continuous drainage for the leak space was started. Subsequently, complete obstruction of the biliary anastomosis remained. Therefore, the percutaneous transhepatic bile drainage (PTBD) tube was inserted. Recanalization by radiologic interventions was attempted several times without success.

In this case, cholangiography showed no anatomical anomaly and communication between the bile ducts of segment II, III, and IV at the occurrence of biliary obstruction as well as at the first transplant operation. Thus, the bile duct of the segment III was reconstructed by intrahepatic cholangiojejunostomy 6 months after LDLT. For this technique, which has been described previously, the bile duct is exposed by dissecting the umbilical fissure, and the division of liver tissue is not required (*3*). However, in the present patient, the bile duct of segment III was not markedly dilated (5 mm in diameter), and thus the process of its sufficient expo-

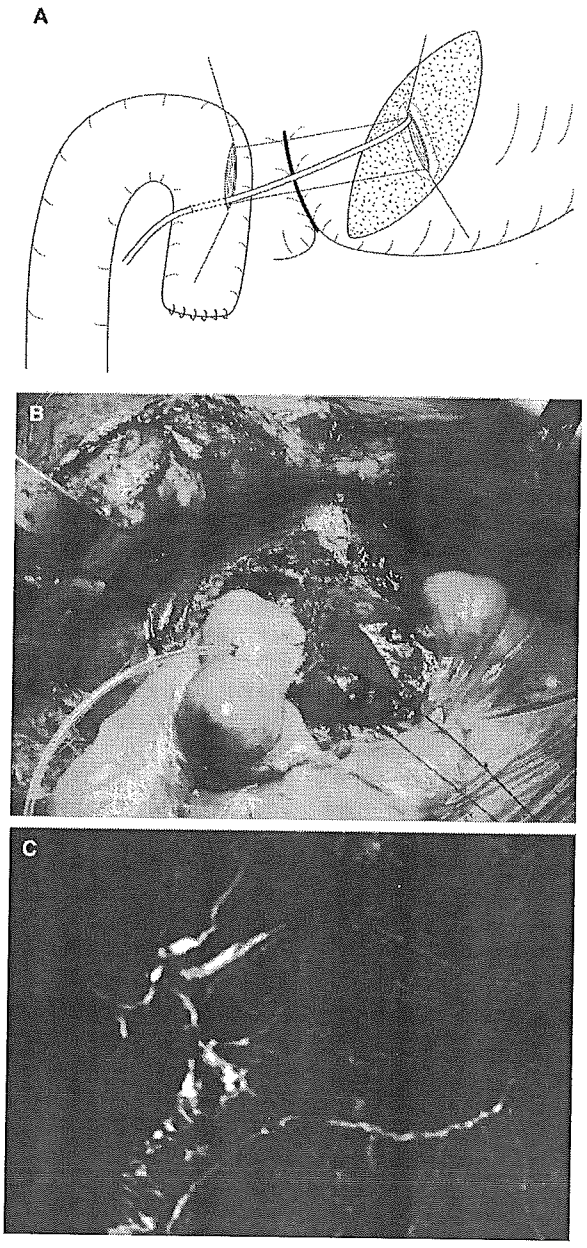

FIGURE 1. Successful treatment of delayed-onset biliary obstruction after left-lobe living-donor liver transplantation (LDLT) by side-to-side intrahepatic segment III cholangiojejunostomy. (A) Schematic view of the procedure. The bile duct of segment III is exposed and incised approximately 3 cm longitudinally. It is anastomosed side-to-side to the Roux-en-Y limb of the jejunum with a 6–0 PDS suture in an interrupted fashion. A 5 F biliary stenting tube is introduced toward the graft hepatic duct from the Roux-en-Y limb of the jejunum. (B) Operative field photograph after completion of the procedure. (C) Magnetic resonance cholangiopancreatography 32 months after the reoperation showing patency of the anastomosis.

sure for anastomosis posed some technical challenges. First, we confirmed the glisson of segment III by using intraoperative ultrasonography and inserted the marking needle toward its proximal site. Along this needle, the liver parenchyma was transected to the left of the round ligament. After the glisson was exposed sufficiently, the bile duct was identified by examining its bulge when the PTBD tube was pressurized. The bile duct was incised approximately 3 cm longitudinally and anastomosed side-to-side to the Roux-en-Y limb of the jejunum with a 6–0 PDS suture in an interrupted fashion. A 5 F biliary stenting tube was introduced toward the graft hepatic duct from the Roux-en-Y limb of the jejunum (Fig. 1, A and B). The patient remained well without biliary complications during the follow-up period of 34 months (Fig. 1C).

Originally, this technique was used as a palliative treatment for obstructive jaundice caused by tumor involvement of the hepatic hilum (*4*). Although conversion to Roux-en-Y hepaticojejunostomy is usually used in the management of biliary obstruction after duct-to-duct anastomosis, it is always accompanied by the risk of injury to the important hilus structures. As for the intrahepatic cholangiojejunostomy, the Longmire technique has been widely recognized. However, it requires partial hepatectomy and is sometimes followed by anastomotic stenosis, especially when a small intrahepatic bile duct is anastomosed end-to-side to the jejunum (*5*). In contrast, this technique has the following advantages. First, it avoids manipulation of the hepatic hilum. Second, the bile duct of segment III is superficially located and easily accessible, and thus the reoperation can be performed at the minimal expense and without hepatic sacrifice. Finally, side-to-side reconstruction offered a sufficient anastomotic size. However, further investigation is necessary to substantiate the value of this technique.

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The United Network for Organ Sharing Position on Using Donors with Primary Central Nervous System Malignancies

In the June 27 issue of *Transplantation*, Buell stated, "Published reports from the United Network for Organ Sharing (UNOS) registry indicated that the use of donors with central nervous system (CNS) malignancies is safe" (*1*). In fact, the conclusion from the reference that he cited (*2*) stated, "The risk of tumor transmission from donors with CNS malignancies seems to be small. Certain tumors, such as glioblastoma multiforme and medulloblastoma, carry a high risk of transmission and should be avoided. The risk of tumor transmission should be weighed against the risk of the patient dying on the waiting list without a transplant. In two subsequent UNOS publications, we stated, however, great caution should be used with donors with glioblastoma multiforme and medulloblastoma because of case reports of transmission of these tumors with organ transplants" (*3*) and "We continue to caution against use of donors with these highly malignant tumors (glioblastoma multiforme and medulloblastoma)" (*4*).

The most recent UNOS data from 1994 to 2003 indicates 28 transmitted tumors in 155,581 cadaveric-organ recipients for a transmission rate of 0.018%. In these 155,581 recipients, there were three deaths from donor-transmitted glioblastoma multiforme (0.002%). During this same time period, there were 44,493 waitlist deaths. Therefore, our position remains: "the risk of tumor transmission should be weighed against the risk of the patient dying on the waiting list without a transplant."

UNOS data from 1994 to 2003 on 174 donors with diagnosis-defined CNS tumors revealed one donor with tumor transmission, for a donor transmission rate of 0.6%. From these 174 donors, there were 528 recipients, and the single donor with tumor transmission fatally affected three recipients, for an organ transmission rate of 0.6%. One hundred sixteen of these 174 donors who had a potentially highly malignant CNS tumor (glioblastoma multiforme, medulloblastoma, astrocytoma) revealed one donor with tumor transmission, for a donor rate of 0.9%. From these 116 donors, there were 358 organ recipients, and the single donor with tumor transmission fatally affected three recipients, for an organ transmission rate of 0.8%. At present, these numbers are not sufficiently large to make a definitive statement regarding the risk of tumor transmission from highly malignant CNS tumors, and UNOS will continue to collect these data and publish it periodically to help transplant surgeons assess the risk of tumor transmission.

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United Network for Organ Sharing Publication on Scientific Registry of Transplant Recipients Central Nervous System Donor Cancer Transmission Data

Dr. Penn would be pleased to note that the stated United Network for Organ Sharing (UNOS) interpretation of Scientific Registry of Transplant Recipients (SRTR) data on the risk of donor central nervous system (CNS) tumor transmission is identical to his initial opinion published in 1991 (*1–4*). The manner in which the overall risk of tumor transmission is reported deserves comment. Data regarding the risk of CNS tumor transmission is only relevant when expressed as the following proportion: the number of transplant recipients who experience donor CNS tumor transmission out of the entire population of transplant recipients who receive organs from donors with CNS tumors. Expression of this risk using other denominators (such as all solid-organ donors) can be misleading because the overwhelming majority of the population is not at risk for donor-related CNS tumor transmission. UNOS presentation of data in this manner only means one thing: that donors with a history of CNS tumors are relatively infrequent, and the risk of transmission of a CNS tumor in most patients with CNS tumors is also infrequent.

UNOS publications have generally held that the risk of tumor transmission in transplant recipients is small. It is small however, because of two reasons. First, donors with CNS tumors are very infrequent. Second, among donors with CNS tumors, those that are high risk for transmission actually represent a minority of this group of donors. The transplant community must be sophisticated enough, however, to understand that a high-risk population does exist and that great care should be used to identify these donors and avoid use of their organs. When this level of sophistication does not exist, the risk of tumor transmission will be real.

Definition of risk factors for tumor transmission requires a critical mass of recipients experiencing these events. For relatively rare events, event-based registries have substantial advantages over mandatory reporting registries, where capture rates are always at issue. The Israel Penn International Transplant Tumor Registry (IPITTR) has the only data set capable of defining risk factors for tumor transmission because it has a substantial number of recipients with donor CNS tumor transmission. In contrast, the paucity of observed donor CNS tumor transmission events in the Australian New Zealand and SRTR registries precludes such analyses. Furthermore, IPITTR collects substantially more detailed information, including pathology reports, and therefore data collected on individual events is substantially more robust. Mandatory reporting registries simply cannot require such detailed reporting from all centers. This issue, more than any other, highlights the importance of both types of registries in answering questions regarding infrequent events such as donor-related CNS tumor transmission.

The importance of defining risk factors for donor CNS tumor transmission arises when a transplant team is under time pressure to make a decision about using organs from a donor with a history of CNS tumor. The IPITTR is consulted relatively frequently on these issues, and the purpose of our ongoing work on this issue is to better define those donors with a history of CNS tumors who represent the highest risk of tumor transmission so we can better advise the transplant community in a consultative setting. The IPITTR is continuing to collect highly detailed data on patients in the United States and the international transplant community on patients receiving organs from donors with a history of CNS tumors to better define those donors at highest risk of tumor transmission. Ongoing updates of these data with scientific publication will improve the consultative services on these donors to the international transplant community.

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Hemorrhagic Cystitis Caused by Adenovirus Type 34 after Allogeneic Bone Marrow Transplantation

Adenovirus (AdV) is one of the pathogens that causes serious infectious complications including hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation (HSCT). The most frequent serotypes of AdV isolated in HSCT recipients developing hemorrhagic cystitis is type 11 (*1*). AdV type 34 was first isolated from the urine of a renal-transplant recipient (*2*). Thereafter, there have been only a few reports of isolated AdV type 34 from humans (*3–5*). We here describe a case of hemorrhagic cystitis caused by AdV type 34 after allogeneic HSCT. To the best of our knowledge, this is the first documented case of hemorrhagic cystitis caused by AdV type 34.

An 18-year-old female with acute leukemia failed to achieve a complete remission by chemotherapy consisting of cytarabine and idarubicin. She then underwent allogeneic bone marrow transplantation from an human leukocyte antigen-matched unrelated donor after being conditioned with total body irradiation and high-dose cytarabine. For the prophylaxis of acute graft-versus-host disease, she received tacrolimus and short-term methotrexate. On day 19, she developed macroscopic hematuria accompanied by urinary urgency. Hemorrhagic cystitis was diagnosed, and she was treated with intravenous antibiotics and hydration. No antiviral agents were administered. Urine cultures failed to grow any bacteria and fungi. AdV was detected in the urine by the shell vial assay and polymerase chain reaction (PCR) designed to detect AdV without a serotype specification. Her urinary symptoms and hematuria completely disappeared within 10 days without any findings of involvement of other organs. Hemorrhagic cystitis did not recur thereafter.

Four-week virus culture of the patient's urine yielded AdV, whose serotype could not be identified by a set of monoclonal antibodies against types 1 to 11. Sequencing of the hexon gene of the clinical isolate from the patient's urine showed a high homology with the prototype AdV type 34 (accession no. AB052911) (99%), which was higher than the homology with type 35 (87–90%). On the basis of these results, the isolated virus was identified as AdV type 34 and as the causative pathogen of hemorrhagic cystitis.

The clinical manifestations of AdV infection after allogeneic HSCT are hemorrhagic cystitis, gastroenteritis, nephritis, pneumonitis, and hepatitis. AdV type 11 is the commonest type to cause hemorrhagic cystitis, although other types have also been isolated (*1*). In this case, AdV was detected in the urine by shell vial assay and conventional virus culture as well as PCR assay. However, the immunofluorescent-antibody technique using monoclonal antibodies against 11 serotypes of AdV (types 1–11) failed to determine the serotype of isolated AdV. Amino acid sequences of isolated virus showed the highest homology with type 34. On the basis of these findings, we concluded that hemorrhagic cystitis in this case was caused by AdV type 34.

AdV type 34 was first isolated from a renal-transplant recipient with persistent fever and liver dysfunction in 1975 (*2*). Since the first isolation, there have been only four reports of isolation and identification of AdV type 34 in humans (*3–5*). These include a report of another renal-transplant recipient with pneumonia and one showing the isolation of AdV type 34 from the urine of AIDS patients (*3, 4*). Uchio et al. (*5*) recently reported two immunocompetent patients developing conjunctivitis caused by AdV type 34. To the best of our knowledge, this is the first reported case of hemorrhagic cystitis caused by AdV type 34. Previous reports and this case support the fact that AdV type 34 could cause a wide spectrum of invasive diseases not only in immunocompromised subjects but also in immunocompetent ones. We conclude that AdV type 34 has a potential to cause hemorrhagic cystitis in immunocompromised patients, and physicians should attempt to identify AdV type 34 in cases of failure to identify other common types in adenoviral hemorrhagic cystitis.

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Small-for-Size Syndrome after Living-Donor Liver Transplantation Treated by "Portal Vein Wrapping" and Single Plasmapheresis

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With the increasing use of living-donor liver grafts in adult patients, small-for-size syndrome became an important clinical problem (*1*). Its occurrence appears to depend on a number of recipient and graft factors. Potential pathogenic mechanisms include persistent portal hypertension and portal over-perfusion (*2*). At present, several techniques are being explored in an attempt to ameliorate the impact of small-for-size syndrome (*3*).

A 47-year-old man, 196 cm tall and 78 kg in weight, suffering from end-stage hepatitis B cirrhosis, underwent living-donor liver transplantation (LDLTx) in our center. His own liver had a calculated volume of 1,639 mL as shown by native liver computer tomography (CT) and was replaced by the right hemiliver of his brother, which had a calculated native volume of 935 mL as shown by three-dimensional CT. A graft-recipient weight ratio of 0.8% was measured preoperatively. Intraoperatively, after an uneventful right hepatectomy of the donor according to the virtual intervention planning, the right graft was weighed at 719 g. To reduce the portal vein over-perfusion and to prevent a small-for-size syndrome in the recipient, a "portal vein-wrapping" with Tabotamb (regenerated oxidized cellulose mesh with local hemostatic ability) was performed intraoperatively. On the first postoperative day, the patient underwent a second laparotomy under the suspicion of hepatic artery thrombosis, which was not confirmed. Over the next 3 days, the patient developed liver dysfunction (elevation of total bilirubin from 4.4 to 31.2 mg/dL, increased prothrombin time [PT]) and increasing encephalopathy, although the other enzymes (ASAT, ALAT, LDH) showed a regular clinical course. A decision to implement plasmapheresis was made. The procedure was well tolerated by the patient, who remained hemodynamically stable throughout the treatment period. Serum levels of total bilirubin and PT as well as encephalopathy were significantly improved after the first session of plasmapheresis.

Because of significant clinical improvement after the first session, plasmapheresis was not repeated. The patient left the intensive care unit on postoperative day 12. Liver volume was calculated as 2,137 mL on postoperative day 15. Bilirubin, ASAT, ALT, and coagulation profile returned to a normal range, and the patient was discharged on postoperative day 29 in good physical condition. Twelve months after transplantation, he returned to his everyday activities and is currently in good general condition.

Severe hyperbilirubinemia is known to exert multiple toxic effects. Artificial liver-support devices attempt to bridge patients with fulminant hepatic failure until either a suitable liver allograft is obtained for transplantation or the patient's own liver regenerates sufficiently to resume normal function (*4*). No great experience with liver-transplant patients is available as yet (*5*). The role of repeated sessions of plasmapheresis for primary allograft nonfunction after liver transplantation has been reported (*6*). As our case indicates, even a single plasmapheresis can be an effective treatment for small-for-size syndrome after LDLTx when combined with a surgical modulation of the portal vein inflow such as "portal vein wrapping."

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Variations in Biliary Anatomy Associated with Trifurcated Portal Vein in Right-Lobe Living-Donor Liver Transplantation

Anatomic variations requiring multiple vascular and biliary anastomosis were more frequently seen in right-lobe living-donor liver transplantation (LDLT) than in left lobes, which was explained by the relative consistency between the left umbilical vein and the liver (*1*, *2*). Clinical implications and surgical anatomy of these variations in LDLT, however, has not been studied in detail because of the lack of accumulated experience. Trifurcation of portal venous system, which necessitated dual portal vein anastomosis, occurred in 6.7% of our initial experience with 120 right lobe LDLTs (*3*). Reconstruction using bifurcation of recipient portal vein is feasible in the right-lobe graft with duplicated portal branches and is not a contraindication of right-lobe LDLT.

A relatively high incidence of multiple bile ducts in the patient with trifurcated portal vein was experienced in our series; however, the exact incidence and anatomic relationship have not been analyzed. We report here the incidence of dual portal vein and multiple bile ducts in 321 cases of right-lobe LDLT.

Between June 1990 and April 2004, 972 LDLTs were performed for 947 patients at Kyoto University Hospital. Right-lobe LDLT was first adopted in February 1998, and thereafter, 321 patients received right-lobe graft. Portal and biliary anatomy was confirmed by one experienced radiologist using preoperative three- or two-dimensional computed tomography, intraoperative cholangiography, and intraoperative findings. None of the patients were excluded from the potential donation because of portal and biliary anomaly.

A total of 295 (91.9%) grafts had bifurcated portal vein, and 26 (8.1%) had trifurcated portal vein. Overall, one hundred twenty-six (39.6%) grafts had multiple bile ducts in the series. One hundred nine of 295 (36.9%) grafts showed single portal vein with multiple bile ducts. Eighteen of 26 (69.2%) grafts showed dual portal vein accompanied with multiple bile ducts. Incidence of multiple bile ducts was significantly higher in the graft with dual portal vein ($P=0.001$). The anatomic variation in right-lobe grafts was classified into five types based on tributaries from the posterior segment, which was proposed by Nakamura et al. (*3*) (Fig. 1). The overall incidence of biliary anastomotic leakage and stenosis was 8.4% and 19.5% in our experience with 321 right-lobe LDLTs.

Biliary complications are the most common complications related to LDLT surgery (*4*). When a dual portal vein anastomosis is required, there may be an increased risk of multiple biliary reconstruction in right-lobe LDLT. An understanding of these frequently encountered variations is vital to avoid surgical complications in right-lobe LDLT.

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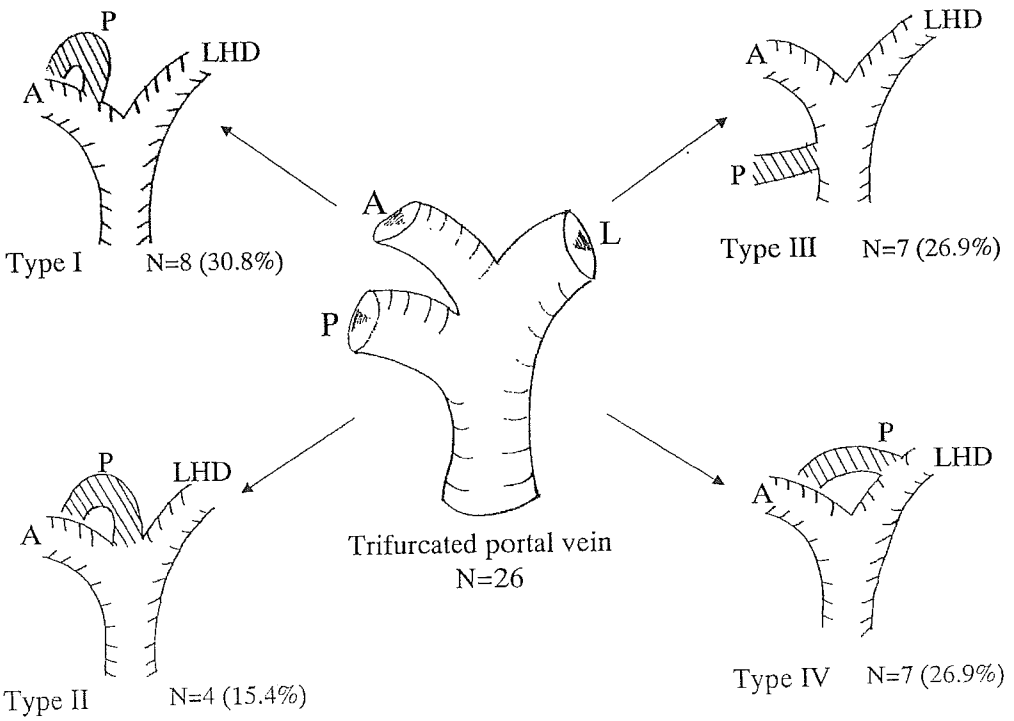

FIGURE 1. Anatomic types of biliary tree in trifurcated portal vein in right-lobe graft defined by tributary from the posterior segment. A, anterior; P, posterior; L, left portal vein; LHD, left hepatic duct.

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REVIEW

Current Role of Liver Transplantation for the Treatment of Urea Cycle Disorders: A Review of the Worldwide English Literature and 13 Cases at Kyoto University

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To address the current role of liver transplantation (LT) for urea cycle disorders (UCDs), we reviewed the worldwide English literature on the outcomes of LT for UCD as well as 13 of our own cases of living donor liver transplantation (LDLT) for UCD. The total number of cases was 51, including our 13 cases. The overall cumulative patient survival rate is presumed to be more than 90% at 5 years. Most of the surviving patients under consideration are currently doing well with satisfactory quality of life. One advantage of LDLT over deceased donor liver transplantation (DDLT) is the opportunity to schedule surgery, which beneficially affects neurological consequences. Auxiliary partial orthotopic liver transplantation (APOLT) is no longer considered significant for the establishment of gene therapies or hepatocyte transplantation but plays a significant role in improving living liver donor safety; this is achieved by reducing the extent of the hepatectomy, which avoids right liver donation. Employing heterozygous carriers of the UCDs as donors in LDLT was generally acceptable. However, male hemizygotes with ornithine transcarbamylase deficiency (OTCD) must be excluded from donor candidacy because of the potential risk of sudden-onset fatal hyperammonemia. Given this possibility as well as the necessity of identifying heterozygotes for other disorders, enzymatic and/or genetic assays of the liver tissues in cases of UCDs are essential to elucidate the impact of using heterozygous carrier donors on the risk or safety of LDLT donor-recipient pairs. In conclusion, LT should be considered to be the definitive treatment for UCDs at this stage, although some issues remain unresolved. (*Liver Transpl 2005;11:1332-1342.*)

Urea cycle disorder (UCD) is one of the most common inborn errors of metabolism in the liver. Although no population studies have been performed, its prevalence is considered to be 1:30,000–46,000 live births.[1,2] Because the urea cycle is the final common pathway for the metabolism of waste nitrogen in humans, a defect of this pathway results in the accumulation of nitrogen as ammonia, glutamate, alanine, and intermediates prior to the metabolic block.[1,2] UCDs are caused by the following deficiencies in enzymes: carbamyl phosphate synthetase I deficiency (CPSID), ornithine transcarbamylase deficiency (OTCD), argininosuccinate synthetase deficiency (ASSD; neonatal onset form, citrullinemia type I [CTLN1]; adult onset form, citrullinemia type II [CTLN2]), argininosuccinate lyase deficiency (ASLD), arginase deficiency (argD), and *N*-acetylglutamate synthetase deficiency (NAGSD).[1,2] Clinical manifestations of these UCDs are determined principally but not only by serum concentrations of ammonia and glutamate with symptoms that range from mild cognitive deficit to deep coma and can range in severity from fatal neonatal hyperammonemia to asymptomatic adults. An approximate determination of which enzymes in the pathway are defective can be established based on quantitative serum amino

Abbreviations: LT, liver transplantation; UCDs, urea cycle disorders; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; APOLT, auxiliary partial orthotopic liver transplantation; CPSID, carbamyl phosphate synthetase I deficiency; OTCD, ornithine transcarbamylase deficiency; ASSD, argininosuccinate synthetase; CTLN1, citrullinemia type I; CTLN2, citrullinemia type II; ASLD, argininosuccinate lyase deficiency; argD, arginase deficiency; NAGSD, *N*-acetyl glutamate synthetase deficiency; QAAA, quantitative serum amino acid analysis; CT, computed tomography; GRWR, graft-to-recipient weight ratio; ACR, acute cellular rejection; PSP, portal steal phenomenon.

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acid analysis (QAAA) profiles, and an enzymatic assay of each enzyme using liver tissue extracted by needle biopsy can lead to a precise determination of the deficient enzyme. Furthermore, the genetic errors responsible for each enzyme deficiency have been almost entirely elucidated, and thus a genetic diagnosis will soon be established.[1,2] Because conservative medical treatments consisting mainly of protein-restricted diet and alternative pathway medication—both of which are intended to prevent an upsurge in serum ammonia—for these disorders have been refined by the recent precise biochemical and molecular recognition given to their pathophysiology, some affected patients have been able to survive for a long time with acceptable quality of life. However, conservative medical treatments are complicated and require close medical supervision to control the risk of severe hyperammonemic coma.[1-4]

Liver transplantation (LT) has played a significant role in the treatment of UCDs.[1-4] However, because of their rare occurrence, there have been no large series studies discussing the outcomes of LT in UCD patients. In this monograph, we examined the current role of LT for the treatment of UCDs by reviewing previously reported cases in the worldwide English literature as well as our single-center experience with living donor liver transplantation (LDLT) in 13 UCD patients.

Patients and Methods

To the best of our knowledge, there have been 38 cases of LT for UCDs reported in the worldwide English literature (Table 1),[5-21] not including our own previously reported cases.[22-24] We reviewed these 38 cases in addition to our 13 LDLT cases (Table 2) to collect the following data: disease, age of onset, gender, time from onset to LT, disease severity, metabolic status, neurological status, timing of LT (elective or emergent), donor (deceased or living), graft type (whole or partial), auxiliary partial orthotopic liver transplantation (APOLT) or not, postoperative complications, survival outcomes, consequences of disease severity, metabolic status, and neurological status. Emergency transplantation was defined as LT that was performed under urgent conditions necessitating artificial ventilation because of severe hyperammonemic coma. With regard to our 13 LDLT cases, we further investigated the following variables: pretransplant status, donor, graft type, graft-to-recipient weight ratio (GRWR), and outcomes of LDLT, including postoperative complications, chronological changes in disease severity, metabolic status, neurological status, and quality of life. Disease severity, metabolic status, and neurological status were assessed by accepted grading scales essentially following Whitington et al.[3] with minor modifications, as shown in Table 3. Quality of life was also classified into 4 subgroups as shown in Table 3.

UCDs are inherited diseases; OTCD is inherited in an X-linked manner and the other 5 disorders in an autosomal recessive manner.[1,2,24] Thus, in cases of autosomal recessive disorders, the parents and offspring of an affected individual were heterozygotes; siblings had a 50% probability of being a heterozygote or a 25% probability of being latently diseased. Furthermore, females with OTCD can inherit causative genetic errors for OTCD from either parent.

With regard to our 13 LDLT cases, the parental donors of 6 girls with OTCD underwent a preoperative allopurinol loading test[25,26] to determine whether each donor was heterozygous. Preoperative donor needle biopsy of the liver used for enzymatic and/or genetic assays was performed when indicated. In addition, the following data were collected for all employed donors: age; relationship to recipient; mode of donor hepatectomy; resection volume (%) of donor hepatectomy calculated by the following formula: resection volume (%) = {(actual graft weight [g])/(total liver volume calculated with preoperative computed tomography [CT] volumetry [ml])} × 100 (%); and postoperative complications, including hyperammonemia. To evaluate the use of a heterozygote as a donor, mortality or morbidity related to the use of heterozygous donors were investigated. In our LDLT cases who were recipients of heterozygous livers, we examined whether hyperammonemia occurred without evidence of graft dysfunction. In addition, we asked both heterozygous donors and recipients of heterozygous livers about the presence of episodes suggestive of hyperammonemia. For previously reported cases, we investigated whether there was a description of mortalities or morbidities associated with the use of heterozygous donors.

With respect to our 13 LDLT cases, follow-up was continued until March 2005 or death for both donors and recipients.

Statistical analysis was conducted in a nonparametric manner using SPSS commercial statistic software (SPSS 12.0. for Windows; SPSS, Chicago, IL) when indicated. Numerical variables are shown as median (range). Survival was evaluated by the Kaplan-Meier life table analysis with the Breslow-Gehan-Wilcoxon test when indicated.

Results

Overall Cases

Patient Characteristics

The indications for LT were OTCD in 22 cases, CTLN2 in 20, CTLN1 in 4, CPSID in 4, and argD in 1 (Tables 1 and 2). The age of onset ranged from 0-62 years, with a median of 31.5 months. Two patients with OTCD were diagnosed prenatally by genetic assays.[21] The time from onset to LT ranged from 0.5-202 months, with a median of 9.0 months. Emergency transplantation was performed in 4 patients (case nos.

Table 1. Results of a Review of the Worldwide Literature Discussing the Outcomes of Liver Transplantation for the Urea Cycle Disorders

Case No.	Disease	Age of Onset	Gender	Age at LT	Donor	APOLT	Posttransplant Remaining Neurological Impairments	Survival Outcomes	Causes of Death	Reference No.
1	OTCD	0 yr 8 months	F	4 yr	Deceased	No	No	42 months, alive		(5)
2	CPSID	2 days	M	1 yr 8 months	Deceased	No	Yes	18 months, died	Pneumonia	(6)
3	OTCD	0 yr 0 months	M	1 yr 2 months	Deceased	Yes	Yes	7 months, died	Biliary stricture	(7)
4	CPSID	2 days	M	14 days	Deceased	No	Yes	40 months, alive		(8)
5	CTLN2	35 yr	M	35 yr 10 months	Deceased	No	No	34 months, alive		(8)
6	OTCD	0 yr 0 months		1 yr 9 months	Deceased	No	No	60 months, alive		(8)
7	OTCD			5 yr	Deceased	No	No	36 months, alive		(8)
8	OTCD			1 yr 8 months	Deceased	No		2 weeks, died	Hospital mortality	(8)
9	OTCD			2 yr 4 months	Deceased	No	Yes	18 months, alive		(8)
10	OTCD				Deceased	No				(9)
11	OTCD				Deceased	No				(9)
12	CTLN1				Deceased	No				(9)
13	OTCD	21 days	F	5 yr	Deceased	No	No	24 months, alive		(10)
14	OTCD	1 day	M	80 days	Deceased	No	No	6 months, alive		(10)
15	CTLN2	38 yr	M	39 yr	Deceased	No	No	12 months, alive		(11)
16	OTCD	2 days	M	0 yr 3 months	Deceased	No	No	63 months, alive		(12)
17	OTCD	0 yr 0 months	M	0 yr 7 months	Deceased	No	Yes	39 months, alive		(12)
18	OTCD	0 yr 0 months	M	40 days	Deceased	No	No	9 months, alive		(12)
19	CTLN	13 days	M	12 yr	Deceased	No	No	29 months, alive*		(13)
20	CTLN2	60 yr 0 months	F	60 yr 4 months	Living	No	No	13 months, alive		(14)
21	CTLN2	15 yr 6 months	M	16 y 0 m	Living	No	No	72 months, alive†		(15)
22	CTLN	10 yr 0 months	F	6 yr 0 months	Living	No	No	18 months, alive		(16)
23	ARD	0 yr 2 months	F	7 yr 0 months	Deceased	No	No	26 months, alive		(17)
24	CTLN2	12 yr	F	21 yr 0 months	Living	No	Yes	39 months, alive		(18)
25	CTLN2	61 yr 4 months	F	62 yr 0 months	Living	No	No	12 months, alive		(18)
26	CTLN2	25 yr 0 months	M	25 yr 7 months	Living	No	No	70 months, alive		(18)
27	CTLN2	44 yr	M	45 yr	Living	No	No	55 months, alive		(18)
28	CTLN2	23 yr	F	24 yr	Living	No	No	37 months, alive		(18)
29	CTLN2	17 yr	F	17 yr	Living	No	No	31 months, alive		(18)
30	CTLN2	21 yr	M	32 yr	Living	No	No	19 months, alive		(18)
31	CTLN1	0 yr 1 month	F	0 yr 10 months	Living	No	No	72 months, alive†		(19)
32	CTLN2	32 yr	M	32 yr	Living‡	Yes	No	24 months, alive		(20)
33	CTLN2	40 yr	F	42 yr	Living	Yes	No	22 months, alive		(20)
34	CPSID	0 yr 0 months	M	0 yr 5 months	Deceased	No	No	>30 months, alive		(21)
35	CPSID	0 yr 0 months	M	0 yr 3.5 months	Deceased	No	Yes	>30 months, alive§		(21)
36	OTCD	0 months |	M	0 yr 11 months	Deceased	No	No	>30 months, alive		(21)
37	OTCD	0 months |	M	0 yr 8 months	Deceased	No	No	>30 months, alive		(21)
38	OTCD	2 yr 6 months	F	2 yr 11 months	Deceased	No	No	>30 months, alive		(21)

Abbreviations: LT, liver transplantation; APOLT, auxiliary partial orthotopic liver transplantation; OTCD, ornithine transcarbamylase deficiency; CPSID, carbamyl phosphate synthetase I deficiency; CTLN2, type II citrullinemia; CTLN1, type I citrullinemia, ARD, acute respiratory disease.

*The patient underwent retransplantation 17 months after the initial transplant because of secondary biliary cirrhosis due to biliary anastomotic stricture.

†Personal communication of 2005.2.

‡In this case, domino splitting liver harvested from a patient with familial amyloid polyneuropathy was used for the transplantation.

§The patient was listed for retransplantation because of secondary biliary cirrhosis due to biliary anastomotic stricture.

| These patients had the prenatal diagnosis by the genetic assessment.

Table 2. Thirteen Patients with the Urea Cycle Disorders Who Underwent Living Donor Liver Transplantation at Kyoto University

Case No.	Age at LDLT	Gender	Diagnosis	Time from Onset to LDLT (Months)	Donor	ABO- Blood Type Matching	APOLT	GRWR (%)	Survival Outcomes (Current Immunosuppression)	Pretransplant status (DS/MS/NS)	Status at the Latest Evaluation* (DS/MS/NS)	Quality of Life at the Latest Evaluation*
39	52 yr 7 months	F	CTLN2	202	Husband	Identical	Yes	0.84	92 months, alive (Tacrolimus alone)	4/3/1	0/0/0	Excellent
40	23 yr 6 months	M	CTLN2	10	Brother	Identical	Yes	0.78	77 months, alive (Tacrolimus alone)	4/4/4	0/0/0	Excellent
41	20 yr 3 months	M	CTLN2	38	Father	Compatible	Yes	1.21	1 month, died of sepsis	1/1/1		
42	30 yr 11 months	M	CTLN2 with HCC	15	Father	Compatible	No	1.55	29 months, died of brain metastases of HCC	3/3/0	0/0/0†	Excellent†
43	21 yr 8 months	F	CTLN2	4	Father	Identical	No	1.63	63 months, alive (Tacrolimus alone)	4/3/1	0/0/0	Excellent
44	18 yr 2 months	F	CTLN2	9	Mother	Identical	No	1.42	41 months, alive (Tacrolimus and mizoribine)	2/3/1	0/0/0	Good
45	39 yr 6 months	M	CTLN2	3	Wife	Identical	No	1.36	26 months, alive (Tacrolimus alone)	2/2/0	0/0/0	Excellent
46	2 yr 6 months	F	OTCD	3	Mother	Identical	No	2.67	121 months, alive (Tacrolimus alone)	4/4/4	0/0/0	Excellent
47	3 yr 0 months	F	OTCD	17	Father	Identical	Yes	2.08	118 months, alive (None)	4/4/4	0/0/0	Excellent
48	5 yr 9 months	F	OTCD	36	Father	Identical	Yes	1.34	103 months, alive (Tacrolimus alone)	4/3/1	0/0/0	Excellent
49	4 yr 10 months	F	OTCD	9	Mother	Identical	No	1.51	89 months, alive (Tacrolimus alone)	3/3/1	0/0/0	Excellent
50	7 yr 2 months	F	OTCD	86	Father	Identical	No	1.3	6 months, died in a traffic accident	4/3/1	0/0/0†	Good†
51	16 yr 2 months	F	OTCD	177	Father	Identical	No	0.94	60 months alive (Cyclosporin A alone)	4/3/2	0/0/0	Excellent

Abbreviations: LDLT, living donor liver transplantation; APOLT, auxiliary partial orthotopic liver transplantation; GRWR, graft-to-recipient weight ratio (%); DS, disease severity; MS, metabolic status; NS, neurological status; CTLN2, citrullinemia type II; HCC, hepatocellular carcinoma; OTCD, ornithine transcarbamylase deficiency.
*Assessed by grading scales or classified into subgroups as shown in Table 3.
†Evaluated at the outpatient clinic prior to death.

5, 40, 46, and 47). Whole liver deceased donor LT (DDLT) was performed in 20 cases, partial liver DDLT in 5, and LDLT in 26.

Surgical Outcomes

Among the 51 cases under consideration, there were only two hospital mortalities (case nos. 8 and 41) and 4 other deaths (case nos. 2, 3, 42, and 50). Two of the 4 deaths other than hospital mortalities arose from complications of LT or remaining neurological impairments (case nos. 2 and 3). The other two deaths (case nos. 42 and 50), both of which were among our cases, were unrelated to either the LDLT procedure or to the original UCD (Table 4). With respect to the cases taken from the literature, biliary complications were reported to have led to graft failure in three cases. As a result, case 3 died[7]; case 19 underwent a second LT 17 months after the first LT[13]; and case 35 had been placed on a waiting list for retransplantation.[21] Other than these three cases and the two cases of hospital mortality, no serious postoperative complications leading to mortalities or graft losses were observed. Based on our analysis, the cumulative posttransplant graft and patient survival rates were 93.7% and 93.7% at 1 year, and 88.9% and 91.3% at both 5 and 10 years, respectively (Fig. 1).

Metabolic and Neurological Outcomes After Liver Transplantation

Hyperammonemia, dietary restrictions, and the use of alternative pathway medications were completely eradicated by LT in all surviving patients, although neurological impairments remained in 7 (case nos. 2, 3, 4, 9, 17, 25, and 35) of the 47 patients in whom neurological status was evaluated. Six of these 7 (case nos. 2, 3, 4, 9, 17, and 35) received LT in their early infancy, at an age ranging from 0.5-28 months with a median of 10.5 months, and the remaining patient (case 25) was a 52-year-old adult. Among the 47 patients in whom neurological status was evaluated, 6 of the 21 patients who underwent DDLT showed remaining neurological impairments, compared with only one of 26 LDLT cases. In other words, neurological impairments were more likely to remain in pediatric cases (6 of 25 cases) than in adult cases (aged 12 years or more, 1 of 22 cases) and more likely to remain in patients who underwent DDLT than in those who underwent

Table 3. Grading Scales to Evaluate Disease Severity, Metabolic Status, and Neurological Status, and Classifications of Quality of Life

Severity of the Disease
Grade 4: many episodes of severe hyperammonemic coma, some with NH3* > 300 μmol/L
Grade 3: one to several episodes of hyperammonemic coma, no more than one with NH3* > 300 μmol/L
Grade 2: one to few episodes of hyperammonemic coma, none with NH3* > 300 μmol/L
Grade 1: only one episode of hyperammonemic coma, with NH3* < 300 μmol/L
Grade 0: no episodes of hyperammonemic coma, no NH3*> 100 μmol/L
Metabolic Status
Grade 4: no improvement, severe hyperammonemia, need for constant, full doses of medication
Grade 3: some improvement, moderate hyperammonemia, need for constant medication
Grade 2: major improvement, moderate hyperammonemia, need for some medication for control
Grade 1: almost complete correction, occasional hyperammonemia, with or without need for medication
Grade 0: complete correction, no hyperammonemia, no need for medication
Neurological Status
Grade 5: persistent coma or vegetative state
Grade 4: responds to noxious stimuli, but no social interaction, no ambulation, no communication
Grade 3: limited social interaction, no bipedal ambulation, limited communication through gestures
Grade 2: definite social interaction, fair ambulation, though possibly limited by spasticity
Grade 1: good social interaction, full ambulation but perhaps partially impaired gross and fine motor skills, use of language, mildly delayed development, only modest learning deficits
Grade 0: seems to be normal spectrum for social interaction, motor skills, language development and learning
Quality of Life
Excellent: receiving one or no immunosuppressive drugs and all the above grading scales corresponding to a score of 0
Good: receiving two or more immunosuppressive drugs and all the above corresponding to a score of 0
Fair: regardless of the number of immunosuppressive drugs each patient received, one or more of the above scales corresponding to a scale of 1
Poor: with any episodes of graft dysfunction to necessitate frequent or long hospital stay regardless of their causes and/or one or more of the above scales corresponding to a score of 2 or more

*Serum ammonia level.

LDLT; these differences did not reach the level of statistical significance.

Outcomes of Auxiliary Partial Orthotopic Liver Transplantation

Although APOLT is considered to be the preferred treatment for UCD,[7,20,22] it was performed in only 8 cases (case nos. 3, 32, 33, 39, 40, 41, 46, and 47). Of these 8 cases, a deceased donor was used in only 1 case (case 3, Table 1), and LDLT was performed in the other 7 cases (Tables 1 and 2). Comparison of posttransplant patient survival between the APOLT cases and the other 43 non-APOLT cases showed that the cumulative patient survival rates were 75.0% at each of 1, 5, and 10 years in the APOLT cases, and 95.0% at 1 year, 92.1% at 5 years, and 92.1% at 10 years in the non-APOLT cases (Fig. 2). There were no statistically significant differences in these rates between the two groups.

Kyoto University Cases

Of our 13 cases, 5 patients underwent APOLT, using a left liver graft (segments II-IV according to Couinaud's Nomenclature for liver segmentations) or left lateral section liver graft (segments II-III); the remaining 8 patients underwent total hepatic replacement (Table 2). Serum ammonia levels fell to the normal range (11-35 μmol/L) within 4 days posttransplant in all patients. Several early postoperative complications were observed, most of which were managed with medication or surgical and/or radiological intervention, resulting in recovery in all patients but one (case 41), who died of sepsis following steroid pulse therapy for acute cellular rejection (ACR) diagnosed in the early postoperative period. Two other deaths (case nos. 42 and 50) were unrelated to the LDLT procedure (Table 2). With regard to long-term complications, late-onset ACR was observed in case nos. 39, 40, 47, and 48, and biliary anastomotic stricture was observed in case nos. 39 and 46. In case nos. 47 and 48, both of whom underwent APOLT, we observed the portal steal phenomenon (PSP), in which late-onset ACR was a trigger and the native liver remnant stole portal blood inflow from graft liver,[24] resulting in mild but refractory hyperammone-

Table 4. Characteristics of the 13 Employed Donors

Case	Recipient's Disease	Relationship with Recipient	Age	Heterozygote or Not	Mode of Donor Hepatectomy	Resection Volume (%) of Donor Hepatectomy*	Duration from Surgery
39	CTLN2	Husband	52	Nonheterozygote	Left hepatectomy†	33.2	92 months
40	CTLN2	Brother	24	Heterozygote or latently diseased	Left hepatectomy†	32.9	77 months
41	CTLN2	Father	54	Heterozygote	Left hepatectomy†	36.7	68 months
42	CTLN2	Father	59	Heterozygote	Right hepatectomy‡	53.2	65 months
43	CTLN2	Father	50	Heterozygote	Right hepatectomy‡	60.8	63 months
44	CTLN2	Mother	54	Heterozygote	Right hepatectomy‡	43.5	41 months,
45	CTLN2	Wife	38	Nonheterozygote	Right hepatectomy‡	64.4	26 months
46	OTCD	Mother	32	Heterozygote	Left lateral sectionectomy§	25.5	121 months
47	OTCD	Father	36	Nonhemizygote	Left lateral sectionectomy§	21.5	118 months
48	OTCD	Father	36	Nonhemizygote	Left lateral sectionectomy§	21.5	103 months
49	OTCD	Mother	35	Heterozygote	Left lateral sectionectomy§	22.1	89 months
50	OTCD	Father	29	Nonhemizygote	Left lateral sectionectomy§	24.1	63 months
51	OTCD	Father	44	Nonhemizygote	Left hepatectomy†	33.2	60 months

Abbreviations: CTLN2, citrullinemia type II; OTCD, ornithine transcarbamylase deficiency.
*Calculated from the following equation: {actual graft weight (g)}/{total liver volume calculated from preoperative CT volumetry (mL)} × 100 (%).
†Resection of segments II+III+IV according to Couinaud's nomenclature for liver segmentation.
‡Resection of segments V+VI+VII+VIII.
§Resection of segments II+III.

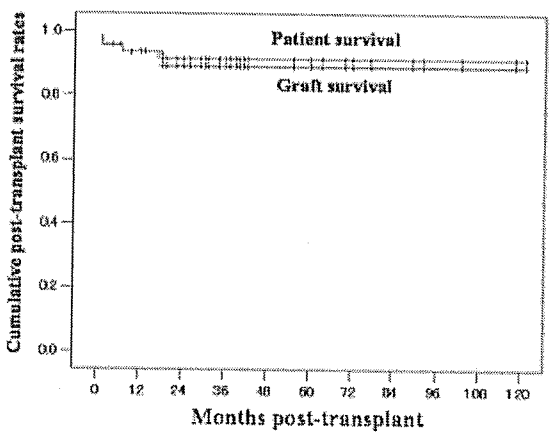

Figure 1. Cumulative posttransplant patient and graft survival rates in 51 patients with urea cycle disorders undergoing liver transplantation. Based on the present analysis, the cumulative posttransplant graft and patient survival rates were 93.7% and 93.7% at 1 year and 88.9% and 91.3% at both 5 and 10 years, respectively.

mia (100-200 μmol/L). In both cases, ligation of the right portal vein flowing into the native liver remnant successfully eradicated the PSP; ligation was performed at 26 months after LDLT in case 47 and at 16 months after LDLT in case 48. In case 48, however, a second PSP was brought on by abundant collateral vessels, which had developed around the previously ligatured right portal vein. As a result, case 48 underwent surgical removal of the native liver remnant at 64 months after LDLT.[24] These complications temporarily impaired the patients' quality of life, but all patients recovered after management with medications or surgical and/or radiological intervention. Consequently, all patients but case 41, in which LDLT resulted in hospital mortality, showed excellent or good quality of life at the latest evaluations (Table 2).

The postoperative observation period of the survivors ranged from 26-121 months, with a median of 77 months (Table 2). No surviving pediatric case has shown any evidence of problematic retardation in neurodevelopmental or physical growth, and all have been

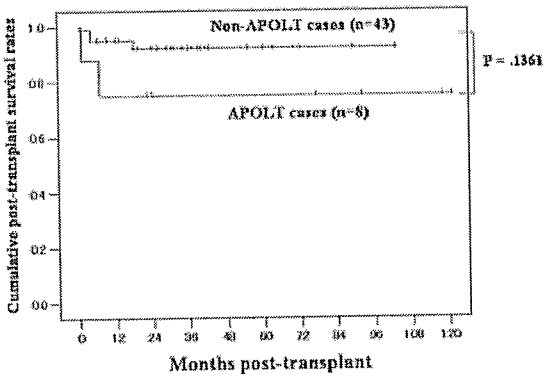

Figure 2. Comparison of cumulative posttransplant patient survival rates between auxiliary partial orthotopic liver transplantation (APOLT) cases and non-APOLT cases. The comparison of posttransplant patient survival between the 8 APOLT cases and the other 43 non-APOLT cases showed that the cumulative patient survival rates were 75.0% at each of 1, 5, and 10 years in the APOLT cases and 95.0% at 1 year, 92.1% at 5 years, and 92.1% at 10 years in the non-APOLT cases. There were no statistically significant differences in these rates between the two groups.

educated at ordinary schools. All surviving adult patients are currently doing well and leading socially normal daily lives. A comparison of cumulative posttransplant patient survival rates between the 13 UCD patients who underwent LDLT and 909 patients undergoing initial LDLT for other indications during the same study period at Kyoto University showed that these rates were better in the 13 UCD patients than in the other 909 patients, although these differences did not reach the level of statistical significance (Fig. 3).

Impact of Employing a Heterozygote as a Donor

Preoperative allopurinol loading testing for parental donors of girls with OTCD (case nos. 46-51) showed 4 fathers with no abnormal findings and two mothers with almost twice the normal upper values of urine orotic acid and orotidine peak levels after the loading. These results suggested that these two mothers were heterozygotes for OTCD. Thus, of 26 living donors, 14 parental and two offspring donors were heterozygous for the disorder in question, two sibling donors had a 50% probability of being heterozygous or a 25% probability to be latently diseased, and the other 8 donors were nonheterozygous.

Irrespective of their status as heterozygous or nonheterozygous, all donors in our LDLT cases (Table 4) fulfilled our standard donor selection criteria as described in detail elsewhere.[27,28] Concerning the heterozygote donors in our cases, three fathers (case nos. 41-43) and one mother (case 44) of CTLN2 patients showed neither elevation in plasma ammonia level nor abnormal QAAA profiles, and all were used as donors without further examinations. In case 40, because a 24-year-old brother of this CTLN2 patient was the only donor candidate, enzymatic assays using liver needle biopsy specimens were performed despite the donor's normal QAAA profiles and lack of elevation in serum ammonia level. The assays showed 30% of the normal value for argininosuccinate synthetase activity, suggesting that the brother was certainly either heterozygous or latently diseased. A genetic assay was not performed because the causative genetic errors of CTLN2 were not well understood at that time.[29] Because the recipient's condition necessitated emergency transplantation, the brother was used as a donor with a strict informed consent clearly stating the potential risks related to his heterozygosis or latent disease. We performed APOLT using a left liver graft in this case in order to avoid right liver donation so as to decrease the operative risks of the donor by reducing the

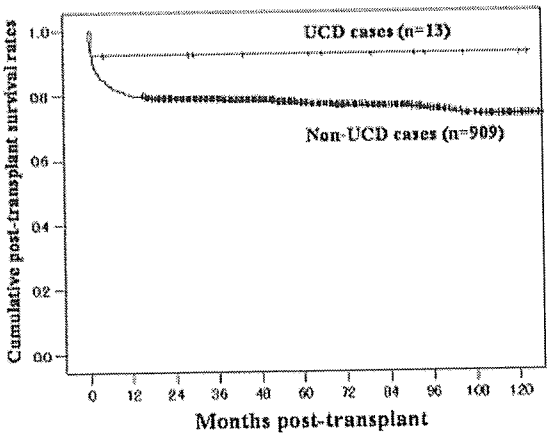

Figure 3. Cumulative posttransplant patient survival rates of 13 patients who underwent living donor liver transplantation (LDLT) and 909 patients who underwent LDLT for other indications during the same study period at Kyoto University. The comparison of cumulative posttransplant patient survival rates between the 13 UCD patients who underwent LDLT and 909 cases undergoing initial LDLT for other indications during the same study period showed that these rates were better in the 13 UCD cases than in the other 909 cases, although these differences did not reach the level of statistical significance. (Two deaths unrelated to LDLT procedures or the original UCD were excluded from the incidence of survival curve of the 13 UCD patients.)

extent of his hepatetomy.[20] Two mothers of girls with OTCD (case nos. 46 and 49), both of whom were determined to be heterozygous for OTCD as stated above, were further examined by enzymatic and genetic assays and proven to be heterozygous for mutations on Xp21, where the OTC gene lies,[1,2,24] but normal in OTC activity in the liver.

In case nos. 42-44, we performed right liver donation for heterozygous carriers; no major postoperative complications occurred in any donors, and all donors were uneventfully discharged from the hospital within 14 postoperative days. None of the donors showed consistent signs of hyperammonemia in the early postoperative period, and all have been doing well without any episodes suggestive of hyperammonemia. Furthermore, all recipients, including those who received heterozygous livers, have shown no episodes of either hyperammonemia without evidence of graft dysfunction or episodes suggestive of hyperammonemia.

With respect to the use of heterozygous donors in our review of the literature, there were no descriptions of mortality or morbidity related to the use of heterozygous donors.

Discussion

In the present metaanalysis, 40 of 51 patients are currently surviving with satisfactory quality of life obtained from the implementation of LT, and neurological impairments remain in 5 surviving patients. The cumulative patient survival rates are presumed to be more than 90% at 5 years posttransplantation. These outcomes are superior to those reported in cases of LT for other diseases.[30] Successful conservative treatment of severely affected UCD patients requires close medical supervision and may become complicated with a high number of medications and strictly restricted protein intake; nevertheless, anecdotal evidence suggests that these patients fare no better than those who undergo LT, and they are always accompanied by the fear of sudden fatal metabolic crisis.[1-4] Thus, LT should be more enterprisingly performed for cases of UCD because the results of the present study confirm that acceptable survival outcomes and quality of life for patients with UCD can be obtained through LT. In addition, a delay in LT for affected patients often leads to remaining neurological impairments, most notably in severely affected infants (case nos. 2, 3, 4, 9, 17, and 24). Furthermore, all individuals affected by UCD run the risk of severe hyperammonemic coma indicative of fatal metabolic crisis, which has been reported to be easily induced by slight stresses such as the common cold.[1-4] In neonatal cases in particular, hyperammonemia with serum levels of more than 300 μmol/L has been reported to easily lead to irreversible brain damage.[2,31] In the early days of both DDLT and LDLT, severely affected neonates rarely received LT due to their small body size and the scarcity of livers of appropriate size.[7,32] In modern times, however, splitting the liver has become a common procedure. In addition, monosegmental liver graft has been gaining wider acceptance even for premature neonates.[32] When DDLT is unavailable, LDLT is an ideal alternative to DDLT when a monosegmental graft is necessary because the donor hepatectomy is less invasive. At present, when the causative genetic errors of UCD have almost been clarified,[2] making prenatal diagnosis possible,[2,19,21,29] elective LDLT immediately after birth can be performed as occasions demand. For adult patients, right liver donation from a living donor has gained wider acceptance[33] and has almost resolved the small-for-size-graft problem.[34] If the extent of right hepatectomy for the donor exceeds 70% of the resection rate, APOLT can be an effective therapeutic option to avoid right liver donation and reduce the extent of donor hepatectomy. Living liver donor morbidity appears to have increased in recent years,[35,36] and this increase in morbidity has been attributed mainly to the wider acceptance of right liver donation.[35] APOLT using a left liver graft can correct UCDs by providing sufficient enzyme supplementation,[20,22] because most UCD livers are functionally normal other than the urea cycle.[1-4] APOLT has traditionally been preferred for the treatment of UCDs because the APOLT recipient will be released from life-long immunosuppressive therapy if gene therapies for the UCDs are established,[37] or if the graft liver is severely damaged, hepatocyte transplantation can be a successful alternative to hepatic retransplantation.[38] However, both of our first two APOLT cases (case nos. 47 and 48) suffered severe graft dysfunction caused by functional competition of portal blood inflow between the native liver remnant and the graft liver.[24] After these experiences, we have performed total portal diversion of the native liver remnant in all subsequent APOLT cases to prevent this functional competition.[39] This procedure benefits the graft liver but compromises the integrity of the native liver remnant, and thus these APOLT recipients would not benefit from gene therapies or hepatocyte transplantation even if these advanced therapies were clinically available. Furthermore, the postoperative morbidity rate of APOLT recipients was higher than that of non-APOLT

recipients,[39] and thus we have suspended our APOLT program over the last several years to reconsider the implications of applying APOLT to UCD patients. However, Yazaki et al.[20] report that partial portal diversion of the native liver remnant, in which only the right anterior branch of the portal vein was ligatured, successfully prevented functional competition of portal blood inflow between the graft and the native liver remnant in CTLN2 cases who underwent APOLT using a left liver graft. This refined procedure can lead not only to better living liver donor safety by avoiding the right liver donation but also to reapproval to perform APOLT in patients with noncirrhotic metabolic liver diseases, including UCDs, with the expectation of the establishment of gene therapies or hepatocyte transplantation because the integrity of the native liver remnant will be maintained with portal inflow supplied by the right posterior branch.

In the present study, no negative impacts of the use of heterozygous carriers as donors on either donors' or recipients' postoperative course have been observed to date. Nevertheless, the advisability of using heterozygous carriers as donors should be considered uncertain. Indeed, it was reported that a recipient of a liver harvested from an adult male deceased donor with unrecognized OTCD died as a result of severe hyperammonemia.[40] Male hemizygotes of OTCD can range in severity from fatal neonatal hyperammonemic coma to asymptomatic adults, whereas female asymptomatic heterozygotes of OTCD might be approved for donor candidacy according to the degree of X-inactivation in the liver because X-inactivation has been reported to be correlated with OTC activity only in the liver.[41] Based on these findings, we propose the following guidelines for the use of heterozygous carriers of UCDs as donors. In OTCD, preoperative enzymatic and genetic assay using liver tissue must be performed for all blood relative donor candidates to exclude male hemizygotes from donor candidacy; in addition, these male hemizygotes must be strictly followed up because of the potential risk of sudden metabolic crisis. Adult heterozygous females for OTCD will be employed as donors only if their liver OTC activity is normal. With regard to the other disorders, asymptomatic heterozygous carriers will be employed only if there are no other candidates. In such situations, liver tissue must be extracted for enzymatic and/or genetic analyses. A part of the tissue should be used to investigate the correlation between genetic errors and enzyme activities, and the remainder must be preserved for future analyses to precisely evaluate the impact of the use of heterozygous carriers for disorders on the risk and safety of both donors and recipients. It remains essential to conduct worldwide multicenter studies.

Although the differences did not reach the level of statistical significance, there was a trend in the present study for neurological deficits to persist in pediatric recipients as well as recipients of DDLT. We consider that an ability to schedule surgery, which is one of the biggest advantages of LDLT over DDLT, had a beneficial effect on the posttransplant neurological outcomes of LDLT recipients. In the past, LT has not been readily used for patients with UCDs. The management of patients with CPSID or OTCD who present in the newborn period is known to be difficult.[3] Thus, these patients must undergo LT immediately after the onset. Furthermore, patients in whom dietary restriction and alternative pathway medications are not very effective must be considered as potential candidates for LT. In other words, patients with UCDs in whom repeated hospitalizations as well as hemodialysis or peritoneal dialysis is required to control hyperammonemia should undergo LT as soon as possible. Especially in pediatric patients, long-term dietary restriction almost always leads to growth retardation, and the retardation of growth has been reported to disadvantageously affect the outcome of LT.[42] Therefore, earlier application of LT to pediatric patients with UCDs will be inevitable to prevent both growth retardation and neurological deficits. In addition, when LT is necessary for UCD patients, LDLT can be an important choice of treatment in order to avoid missing the optimal time range for LT.

In conclusion, LT should be considered to be the definitive treatment for UCDs, and thus more enterprising application of this procedure to UCD patients is acceptable. If DDLT is unavailable, the selection of living donors must be initiated immediately. However, the use of heterozygous carriers as LDLT donors for UCD has not yet been validated.

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Living Donor Liver Transplantation For Biliary Atresia Complicated By Situs Inversus: Technical Highlights

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Living-donor liver transplantation (LDLT) has become an established technique to treat children with end-stage liver disease. Biliary atresia (BA), one of the most common indications for liver transplantation in children, can be associated with situs inversus (SI). In the past, the presence of SI has been considered to be an absolute contraindication for liver transplantation because of the technical difficulties. Recently, some reports of successful diseased-donor liver transplantation in patients with BA complicated by SI have been published; however, few reports of that with LDLT exist. The technical difficulties involved with LDLT for such cases have not been described. Herein, we present 4 successful cases of LDLT for BA with SI. Complex anomalies associated with SI, such as a hepatic artery arising from the supraceliac aorta, a preduodenal portal vein, and absence of the retrohepatic inferior vena cava, increase the technical difficulties involved with the operation. Additional caution is required in LDLT because a living-donor graft has short vessels and the availability of vascular grafts from the donor is limited. In conclusion, LDLT for BA complicated by SI can be managed successfully with technical modifications and scrupulous attention. This series represents the largest reported group of patients with BA complicated by SI who underwent a successful LDLT procedure. (*Liver Transpl 2005;11:1444-1447.*)

Situs inversus (SI) is a condition characterized by a mirror image orientation of the abdominal and thoracic viscera relative to the midline. It includes one or more of the following: polysplenia, intestinal nonrotation, preduodenal portal vein, aberrant hepatic arterial supply, and absence of the retrohepatic inferior vena cava. SI is a rare anomaly, with a frequency reported to be between 0.002% and 0.1%.[1] Interestingly, association with biliary atresia (BA) occurs in up to 28% of children with SI.[2]

Although BA is one of the most common indications for liver transplantation, patients with BA complicated by SI have been considered highly questionable candidates because of the technical difficulties.[3] However, several reports of successful diseased-donor liver transplantation (DDLT) in patients with BA complicated by SI have been published recently.[4-6]

Living-donor liver transplantation (LDLT) has become a standard option for pediatric patients. However, there are few reports of a successful use of a living-donor graft for patients with BA and SI. Herein, we present 4 cases of LDLT performed for BA complicated by SI and discuss the necessary operative management, especially technical highlights, for an SI recipient undergoing such liver transplantation.

Patients and Methods

Between June 1990 and June 2004, 1,000 LDLT procedures were performed at Kyoto University, of which 613 were performed on children (younger than 18 years). For all 1,000 LDLT procedures, 415 were for BA and 4 were for BA with SI. All candidates previously underwent a Kasai operation. The diagnosis of SI was established at presentation using radiography and confirmed during surgical exploration, which was performed prior to LDLT.

The entire operative procedure has been described elsewhere.[7] For the donor operation, a left lateral segment graft was used for three cases. After isolation of the left hepatic artery, hepatic duct, and portal branch in the donor, a hepatic parenchyma of the medial segment was transected 5 mm to the right of the falciform ligament without blood inflow occlusion or graft manipulation. A reduced monosegmental graft method, which was recently introduced for small infants to mitigate the problem of large-for-size graft, was used for one case. Briefly, in the recipient operation, following isolation of the hepatic artery (HA) and portal vein (PV), the liver was dissected from the inferior vena cava (IVC) by ligation and dissection of the short hepatic veins without IVC clamping. After dissection and closure

Abbreviations: LDLT, living-donor liver transplantation; BA, biliary atresia; SI, situs inversus; DDLT, diseased-donor liver transplantation; HA, hepatic artery; PV, portal vein; IVC, inferior vena cava; LUQ, left upper quadrant; HV, hepatic vein; V2, vein from segment 2; V3, vein from segment 3.

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Table 1. Patient Profiles During the Pre- and Posttransplant Periods

Patient No.	Age	Weight (kg)	Pretransplant Operative Numbers	Anatomical Abnormalities	GRWR (%)	Donor	Blood Type Combination	Graft Type	Complications	ICU Stay	Hospital Stay	Follow-up Period
1	5 yr	15	5	Polysplenia Absence of IVC Preduodenal PV PHA directly from aorta	1.56	Father	Identical	S2+3	PV stenosis	5 days	77 days	10 yr 10 months, alive
2	2 yr	10.5	2	Polysplenia Malrotation Left-sided IVC Preduodenal PV PHA directly from aorta Dextrocardia	2.28	Mother	Identical	S2+3	Small intestinal perforation PV stenosis	4 days	153 days	3 yr 11 months, alive
3	1 yr 6 months	7.2	1	Absence of IVC	3.1	Mother	Identical	S2+3	None	5 days	44 days	3 yr 11 months, alive
4	9 months	3.6	3	Malrotation	3.27	Mother	Identical	Reduced monosegment	None	22 days	141 days	6 months, alive

Abbreviations: GRWR, graft-to-recipient weight ratio; IVC, inferior vena cava; PV, portal vein; PHA, proper hepatic artery; S2, segment 2; S3, segment 3.

of the right hepatic vein, a total hepatectomy was completed after side-clamping of the IVC to maintain caval blood flow. The liver graft was implanted into the left upper quadrant (LUQ). For vascular reconstruction, we usually use 5-0 Prolene (continuous) for the hepatic vein (HV), 6-0 Prolene (continuous) for the PV, and 8-0 Prolene (interrupted) for the HA. For biliary reconstruction, a choledochojejunostomy with a Roux-en-Y anastomosis was performed in all patients. Full-layer abdominal closure was performed in each. Posttransplant immunosuppression consisted of tacrolimus and low-dose steroids.[7]

Results

Patient profiles during the pre- and posttransplant periods as well as those during the operation are summarized in Tables 1 and 2.

Case 1

A boy underwent a Kasai operation 43 days after birth, which was followed by revision of the hepatic hilum, because of persistent cholangitis. Liver transplantation was scheduled for the deteriorating liver function as well as variceal bleeding at the age of 5 years old. After a hepatectomy, the liver was transplanted in the usual manner, and an interposed graft taken from the inferior mesenteric vein of his father was used for PV reconstruction. The posttransplant course was uneventful. Yearly follow-up revealed PV stenosis 9 years after transplantation, which was shown to be a complete obstruction with portography.

Case 2

A 2-year 4-month-old girl presented with progressive hepatic failure for LDLT. She had a history of BA and underwent a Kasai operation at the age of 2 months. At that time, the patient was noted to have SI with dextrocardia, polysplenia, intestinal malrotation, and a preduodenal portal vein. A left lateral segment graft from her mother was placed in an LUQ. The graft had two independent veins from segments 2 (V2) and 3 (V3), thus two anastomoses were made individually between graft V2 and the common anastomotic stump of the middle and left hepatic veins of the recipient, and between graft V3 and the right hepatic vein of the recipient. An interposed graft taken from the ovarian vein of the donor was used for PV reconstruction. The immediate postoperative course was complicated by a small intestinal perforation, whereas the later course was further complicated by PV stenosis two years after transplantation.