Living Donor Liver Transplantation for Noncirrhotic Inheritable Metabolic Liver Diseases: Impact of the Use of Heterozygous Donors

Daisuke Morioka, Yasutsugu Takada, Mureo Kasahara, Takashi Ito, Kenji Uryuhara, Kohei Ogawa, Hiroto Egawa, and Koichi Tanaka

Background. In living donor liver transplantation (LDLT), the liver donor is almost always a blood relative; therefore, the donor is sometimes a heterozygous carrier of inheritable diseases. The use of such carriers as donors has not been validated. The aim of the present study was to evaluate the outcome of LDLT for noncirrhotic inheritable metabolic liver disease (NCIMLD) to clarify the effects of using a heterozygous carrier as a donor.

Methods. Between June 1990 and December 2003, 21 patients with NCIMLD underwent LDLT at our institution. The indications for LDLT included type II citrullinemia (n = 7), ornithine transcarbamylase deficiency (n = 6), propionic acidemia (n = 3), Crigler-Najjar syndrome type I (n = 2), methylmalonic acidemia (n = 2), and familial amyloid polyneuropathy (n = 1). Of these 21 recipients, six underwent auxiliary partial orthotopic liver transplantation.

Results. The cumulative survival rate of the recipients was 85.7% at both 1 and 5 years after operation. All surviving recipients are currently doing well without sequelae of the original diseases, including neurological impairments or physical growth retardation. Twelve of the 21 donors were considered to be heterozygous carriers based on the modes of inheritance of the recipients' diseases and preoperative donor medical examinations. All donors were uneventfully discharged from the hospital and have been doing well since discharge. No mortality or morbidity related to the use of heterozygous donors was observed in donors or recipients.

Conclusions. Our results suggest that the use of heterozygous donors in LDLT for NCIMLD has no negative impact on either donors or recipients, although some issues remain unsolved and should be evaluated in further studies.

Keywords: Liver transplantation, Organ donation, Noncirrhotic metabolic liver disease, Donor selection, Inherited diseases.

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Liver transplantation has become a well-recognized therapy for hepatic failure resulting from acute or chronic liver disease. It also plays a role in the treatment of certain inborn errors of metabolism that do not directly injure the liver (*1,2*). Due to the unavailability of deceased donors, living donors have been employed as a major organ resource for liver transplantation in Japan (*3,4*). In living donor liver transplantation (LDLT), the donor is almost always a blood relative of the patient. Because most inborn errors of metabolism are inherited, an obligate heterozygous carrier of the recipient's disorder has sometimes been used as a liver donor (*5–8*). For example, in the case of autosomal recessive disorders, the recipient may gain only half of normal enzyme activity when a parent is used as the donor. In this situation, it is difficult to conclude that a heterozygous liver can correct the disorder and that there will be no relapse of the original disease in the long-term postoperative course. Furthermore, the immediate and long-term risks of heterozygous carrier donors have not yet been fully clarified (*5–8*).

From 1990 to 2003, 21 patients underwent LDLT for noncirrhotic inheritable metabolic liver diseases (NCIMLD) at our institution. Although three of these cases have previously been reported (*9–11*), all were evaluated in the present study in order to determine their LDLT outcomes and to clarify the impact of the use of heterozygous donors on the postoperative course of both donors and recipients.

Organ Transplant Unit, Kyoto University Hospital, Kyoto, Japan.
Address correspondence to: Daisuke Morioka, M.D., Ph.D., Organ Transplant Unit, Kyoto University Hospital, 54 Shogoinkawara-cho, Sakyo-ku, Kyoto, 606-8507, Japan.
E-mail: dmorioka@hotmail.com.
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PATIENTS AND METHODS

Twenty-one patients with NCIMLD indicated for LDLT included type II citrullinemia (CTLN2, n = 7), ornithine transcarbamylase deficiency (OTCD, n = 6), propionic acidemia (PPA, n = 3), Crigler Najjar syndrome type I (CNSI, n = 2), methylmalonic acidemia (MMA, n = 2), and familial amyloid polyneuropathy (FAP, n = 1) (Table 1). All were evaluated based on the mode of operative procedure (auxiliary partial orthotopic liver transplantation [APOLT] or not) (*9,12–14*), graft-to-recipient-weight ratio (GRWR), liver donor (blood relative or not), and the immediate and long-term postoperative course.

All of the 21 donors fulfilled our standard donor selection criteria as described in detail elsewhere (*15,16*). Of these 21, 12 donors were considered to be heterozygous carriers for respective recipient's disorder based on the modes of inheritance of the disorders (Table 2): autosomal recessive inheritance for CTLN2 (*1,2,5*), PPA (*10,17*), and CNSI (*1,18*); multifactorial autosomal recessive inheritance for MMA (*19,20*); autosomal dominant inheritance for FAP (*20*); and X-linked inheritance for OTCD (*1, 2, 21*). Parents with autosomal recessive disorders and mothers with X-linked inheritance disorders were considered to be heterozygous carriers (*5–8, 17, 22–24, 25*). Furthermore, the father of an affected patent with

TABLE 1. Patient characteristics

Case	Age (years)	Sex	Diagnosis	Timing of LDLT	APOLT	ABO-blood type	Donor	Outcomes
1	52	F	Citrullinemia type II	Elective	Yes	Identical	Husband	83 months, alive
2	23	M	Citrullinemia type II	Emergent	Yes	Identical	Brother	68 months, alive
3	20	M	Citrullinemia type II	Elective	Yes	Compatible	Father	1 month, died
4	30	M	Citrullinemia type II	Elective	No	Compatible	Father	30 months, with multiple HCC died of recurrent HCC
5	21	F	Citrullinemia type II	Elective	No	Identical	Father	54 months, alive
6	18	F	Citrullinemia type II	Elective	No	Identical	Mother	32 months, alive
7	39	M	Citrullinemia type II	Elective	No	Identical	Wife	17 months, alive
8	2	F	OTCD	Emergent	No	Identical	Mother	112 months, alive
9	3	F	OTCD	Emergent	Yes	Identical	Father	109 months, alive
10	5	F	OTCD	Elective	Yes	Identical	Father	94 months, alive
11	5	F	OTCD	Elective	No	Identical	Mother	80 months, alive
12	7	F	OTCD	Elective	No	Compatible	Father	4 months, died in traffic accident
13	16	F	OTCD	Elective	No	Identical	Father	51 months, alive
14	2	F	Propionic acidemia	Elective	No	Incompatible	Mother	59 months, alive
15	5	M	Propionic acidemia	Elective	No	Identical	Father	30 months, alive
16	1	M	Propionic acidemia	Elective	No	Identical	Father	21 months, alive
17	5	M	Crigler-Najjar type I	Elective	Yes	Compatible	Mother	81 months, alive
18	4 months	M	Crigler-Najjar type I	Elective	No	Compatible	Mother	47 months, alive
19	1	F	Methylmalonic acidemia	Elective	No	Compatible	Father	15 days, died of metabolic stroke
20	12	F	Methylmalonic acidemia	Elective	No	Compatible	Father	2 months, died of aspergillosis
21	58	M	FAP	Elective	No	Identical	Brother	58 months, alive

LDLT, living donor liver transplantation; APOLT, auxiliary partial orthotopic liver transplantation; HCC, hepatocellular carcinoma; OTD, ornithine transcarbamylase deficiency; FAP, familial amyloid polyneuropathy.

an X-linked inheritance disorder has a probability, albeit an extremely low one, of being heterozygous (*25*).

The mothers of the two CNSI cases (Cases 17 and 18) received no specific medical tests because no problem was found in the results of their routine medical examinations, including serum direct and indirect bilirubin levels. Because of surgical risks and the uncertainty of its significance, preoperative donor liver biopsy for use in enzymatic or genetic assays was performed in only one donor. In Case 2 (CTLN2), an enzymatic assay related to a urea cycle disorder (UCD) using a liver needle biopsy specimen was performed for a brother of the recipient, the only donor candidate, and showed 30% of the normal value for argininosuccinate synthetase activity (*5–7*) despite normal quantitative plasma amino acid analysis (QAAA) and normal plasma ammonia level. No genetic assay was performed because the causative genetic errors of the disease were not well understood at that time (*26*). Although the brother may have been latently diseased, we considered him a heterozygous carrier based on the results of his QAAA and employed him as a liver donor with strict informed consent. For all donors, we reviewed the recipient's disease, donor relationship to the recipient, donor age, the mode of donor hepatectomy, immediate and long-term postoperative course, and resection rate of the donor hepatectomy calculated from the following equation: [{actual graft weight (g)}/{total liver volume calculated from preoperative computed tomography volumetry (ml)}] × 100%.

Mortality and morbidity were studied in relation to the use of heterozygous donors, and some recipients of heterozygous livers and some heterozygous donors also underwent specific medical tests in addition to routine checkups, depending on the recipient's disease. Plasma ammonia level measurement was included in the immediate and long-term postoperative routine medical checkups in cases of UCD; QAAA was performed preoperatively (normal profile, normal serum ammonia level in donors), 1, 3, 6, 12 months after LDLT and annually thereafter in cases of CTLN2; an allopurinol loading test (*27,28*) was performed preoperatively and annually after the LDLT in cases of OTCD; and in cases of PPA, plasma propionic acid level measurement was carried out preoperatively (undetectable in donors), blood gas analysis (BGA) was conducted preoperatively to confirm whether metabolic acidosis was present (normal values in both pH and base excess in donors), and routine postoperative blood tests included both plasma propionic acid measurement and BGA. No specific tests were conducted in the CNSI cases. To determine whether postoperative morbidities were related to the use of heterozygote donors, recipients of heterozygous livers were accompanied by their donors or other family members during follow-up and were asked about their preoperative symptoms. Heterozygous donors and other family members were also asked if they suffered symptoms similar to those of the recipients.

Follow-up was continued until April 2004 or death for both donors and recipients.

SPSS commercial statistics software was used for all statistical analyses (SPSS 12.0 for Windows, Chicago, IL), and P values of <0.05 were considered to be significant.

RESULTS

Outcome of LDLT

The patients' characteristics are summarized in Table 1. Cases 2, 8 and 9 underwent emergency LDLT for life-threatening hyperammonemia, and all three required preoperative apheresis therapy including plasmapheresis and continuous

TABLE 2. Characteristics of the 12 heterozygote donors

Case	Recipient's diseases	Relation to recipient	Age (years)	Mode of donor hepatectomy	Resection rate of donor hepatectomy[a]	GRWR (%)[b]	Duration from surgery (months)
2	Citrullinemia type II	Brother	24	Left hepatectomy[c]	32.9	0.78	68
3	Citrullinemia type II	Father	54	Left hepatectomy[c]	36.7	1.21	58
4	Citrullinemia type II	Father	59	Right hepatectomy[d]	53.2	1.55	56
5	Citrullinemia type II	Father	50	Right hepatectomy[d]	60.8	1.69	54
6	Citrullinemia type II	Mother	54	Right hepatectomy[d]	43.5	1.42	32
8	OTCD	Mother	32	Left lateral segmentectomy[e]	25.5	2.08	112
11	OTCD	Mother	35	Left lateral segmentectomy[e]	22.1	1.51	80
14	Propionic academia	Mother	40	Left lateral segmentectomy[e]	22.9	2.72	59
15	Propionic academia	Father	37	Left lateral segmentectomy[e]	19.3	1.27	30
16	Propionic academia	Father	31	Left lateral segmentectomy[e]	22.4	3.37	21
17	Crigler-Najjar type I	Mother	42	Left lateral segmentectomy[e]	20.8	1.23	81
18	Crigler-Najjar type I	Mother	33	Left lateral segmentectomy[e]	30.9	4.93	47

[a] Calculated by: [(actual graft weight (g))/(total liver volume calculated from preoperative CT volumetry (ml))] × 100%.
[b] Graft-to-recipient weight ratio calculated by [(actual graft weight (g)/ (recipient's body weight (g))] × 100%.
[c] Resection of segments II + III + IV according to Couinaud's nomenclature for liver segmentation.
[d] Resection of segments V + VI + VII + VIII.
[e] Resection of segments II + III.
OTCD, ornithine transcarbamylase deficiency.

hemodiafiltration immediately prior to surgery. The other 18 patients underwent LDLT electively and required no apheresis therapy.

APOLT was performed in six recipients, in whom a left liver (segments II-IV according to Couinaud's nomenclature for liver segmentation) or left lateral segment liver (segments II-III) graft was implanted orthotopically following native left hepatectomy with caudate lobe resection (segments I-IV). In Case 1, APOLT was implemented in order to intend to compensate for the relatively small graft (GRWR was 0.84% in this case) (*29*); it was also implemented in expectation of the future establishment of gene therapies (*30*) or hepatocyte transplantation (*31*) because our institution did not have a right liver donation program from living donors at that time (*32*). In Case 2, the donor had a 100% probability of being a heterozygous carrier or even latently diseased. Thus we applied APOLT to this case to avoid right liver donation; this decreased the operative risks to the donor by reducing the extent of donor hepatectomy (*33*). As for the other four cases, we applied APOLT to these cases with the expectation of future establishment of gene therapies or hepatocyte transplantation. There was no statistical difference between the 5-year survival rates of the APOLT group (83.3%) and the non-APOLT group (78%).

There were five postoperative deaths among recipients, three of which were related to the LDLT procedure. Case 3 died of sepsis, Case 19 of metabolic stroke (*23*), and Case 20 of pulmonary aspergillosis. The other two patients died of brain metastases from hepatocellular carcinoma (Case 4) and a traffic accident (Case 12). The overall cumulative survival rate of all 21 patients was 80.0% at 1 year after operation and 75.6% at 5 years (Kaplan-Meier life table analysis). Excluding the deaths unrelated to LDLT, the cumulative survival rates were 85.7% at both 1 year and 5 years.

Impact of Employing a Potential Obligate Carrier as a Donor

The donors were the father in 11 cases, the mother in 6, a brother in 2, and a spouse in 2 cases; thus a total of 19 patients received grafts from a blood relative (Table 1), 12 of whom (5 fathers, 6 mothers, and 1 brother) were considered heterozygous donors based on the mode of inheritance of the disorder in question (Table 2). Four fathers of patients with OTCD (Cases 9, 10, 12, and 13) also had various probabilities of being heterozygous. However, their results in the allopurinol loading test showed no abnormal findings, and thus we did not consider them heterozygotes. As stated above, additional preoperative medical tests for heterozygote donors showed no unusual findings for either the CTLN2 cases or the PPA cases. Two mothers of OTCD patients proved to be partially deficient in ornithine transcarbamylase based on the results of the allopurinol loading test, in which peak values of urine orotic acid and orotidine were almost twice normal upper values after allopurinol loading (*27,28*), despite normal plasma ammonia levels. Nevertheless, both were used as liver donors because there were no other available donors. Both underwent enzymatic and genetic assays using liver tissue extracted during donor surgery and were proven heterozygous for mutations at Xp21, where the ornithine transcarbamylase gene is located (*22,25*), even though their OTC activity was normal in the liver tissue and neither showed relevant symp-

toms either preoperatively or early in the postoperative period (*2,5,22*). The mothers of the two CNSI patients also showed no symptoms related to their respective heterozygosis. Enzymatic or genetic assays using liver tissue extracted during donor surgery were performed only in Cases 2, 8 and 11, because the significance of these investigations was considered uncertain at that time.

The age of the donors at LDLT, the mode of donor hepatectomy, and resection rate of donor hepatectomy are shown in Tables 2 and 3 for heterozygous and nonheterozygous): donors, respectively. There were no statistical differences in these variables between the two groups, and there were no major complications in any donors. All 21 donors were uneventfully discharged from the hospital within 14 postoperative days; they returned to their preoperative normal daily lives within 2 months of surgery and are currently doing well. Furthermore, there have been no cases to date of any symptoms possibly arising from the heterozygosis, including episodes of hyperammonemia in the cases of UCD, metabolic acidosis in the cases of PPA, or jaundice in the cases of CNSI.

Of the 12 patients who were matched with heterozygous donors, none has shown any evidence of recurrence of the original disease. The 10 survivors of these 12 recipients have not required any dietary restriction during long-term follow-up, although the three PPA patients still receive carnitine supplementation (*10,17*). No statistical difference was found between the survival rates of recipients of heterozygous livers and nonheterozygous livers, with 82.5% survival in the former and 77.8% in the latter at 5 years after operation. Although episodes of hyperammonemia secondary to graft dysfunction due to rejection were observed in Cases 1, 2, 9 and 10 (all of whom underwent APOLT), there have been no episodes of complications arising from the use of a heterozygous donor.

Heterozygous donors to CTLN2 recipients have shown neither abnormal profiles in QAAA nor any episodes suggestive of hyperammonemia or actual hyperammonemia to date. CTLN2 recipients of heterozygous livers have shown no abnormal QAAA profiles and have suffered no episodes of hyperammonemia except Case 2, whose QAAA profile included high levels of citrulline and glutamate during several episodes of hyperammonemia secondary to graft dysfunction due to rejection.

Annual allopurinol loading tests of OTCD Cases 8 and 11, who received heterozygous livers, have shown peak values of urine orotic acid and orotidine excretion of 1.5- to 3-times normal upper values in both donors and recipients. However, there have been neither episodes of hyperammonemia nor episodes suggestive of hyperammonemia in donors or recipients.

Finally, there have been no episodes of metabolic acidosis in PPA recipients or their donors, and no episodes of jaundice have been observed in the CNSI cases. Thus, neither mortalities nor morbidities related to heterozygosis have been observed in either donors or recipients. Regardless of whether or not heterozygous donors were used, no surviving pediatric recipients have shown any problematic retardation in physical growth or neurological impairments. All surviving adult recipients are currently enjoying their normal daily lives as before the onset of the original disease. In addition, all of surviving patients and their families including donors currently declare their well-being and their feeling to be cured.

DISCUSSION

Even when the recipient's disease is known to be inheritable, a blood relative who is heterozygous for the disorder must sometimes be used as a liver donor for LDLT in Japan or other countries where the deceased donors are usually unavailable. It is therefore extremely important to understand the risks of LDLT with heterozygous donors. In the present study, no negative impact was found on the immediate or long-term postoperative courses of either donors or recipients. Although 3 of the 12 heterozygous donors underwent right hepatectomy, which is considered to induce a considerable regenerative process in the donor remnant liver, they showed no serious difficulties either early postoperatively or during long-term follow-up. Regardless of the use of heterozygous or nonheterozygous donors, LDLT produced acceptable survival outcomes with a cumulative survival rate of 85.7% at 5 years after operation and excellent quality of life for all NCIMLD cases. We therefore believe that more extensive use of LDLT is acceptable in the treatment of NCIMLD.

On the other hand, the onset mechanisms of most cases of NCIMLD are not yet completely understood, and some acquired genetic mutations in heterozygous liver may cause a recurrence or new onset of the original disease (*6-8,10,18,19,21,25,26,34,35*). For example, in a study by Saheki and Kobayashi, some CTLN2 cases were caused by the additional effects of genetic or environmental modifiers in the heterozygous carriers (*35*). In addition, it was reported that a recipient of a liver harvested from an adult male deceased donor who had unrecognized OTCD could die as a result of hyperammonemia (*36*). In the present study, liver tissues were not extracted during donor surgery for cryopreservation and future examination, and certain types of study are therefore not possible with the present group of subjects. Most of the genetic mutations of these inborn errors of metabolism are already known and their roles have been clarified (*8,17,18,20–22,25,26,34–36*), even if not completely understood. Because the number of our cases was small and the diseases varied, further follow-up and more studies are necessary to confirm the efficacy and safety of LDLT with heterozygous livers. Therefore, in cases of LDLT for these inborn errors of metabolism with the use of heterozygotes as donors, hereafter the liver tissue must be extracted from both donors and recipients in order to elucidate the impact that the use of the heterozygotes as donors would have on the risk or safety of both donors and recipients. This is because enzymatic and genetic assays using a part of the liver tissue should be mandatory for the recognition of correlations between enzymatic and genetic variations. Moreover, the remainder of the liver tissue must be preserved for more advanced analyses in the future.

Most NCIMLDs arise from enzyme deficiencies, and enzyme supplementation can sometimes correct the disorders (*9,12–14*). APOLT has thus been widely indicated, and indeed, 6 of the 21 patients in the present study underwent APOLT. APOLT recipients will be released from life-long immunosuppressive therapy and maintained with their own liver when gene therapies for these disorders become clini-

TABLE 3. Characteristics of the nine nonheterozygote donors

Case	Recipient's diseases	Relation to recipient	Age (years)	Mode of donor hepatectomy	Resection rate of donor hepatectomy[a]	GRWR (%)[b]	Duration from surgery (months)
1	Citrullinemia type II	Husband	52	Left hepatectomy[c]	33.2	0.84	83
7	Citrullinemia type II	Wife	38	Right hepatectomy[d]	64.4	1.36	17
9	OTCD	Father	36	Left lateral segmentectomy[e]	21.5	2.08	109
10	OTCD	Father	36	Left lateral segmentectomy[e]	21.5	1.34	94
12	OTCD	Father	29	Left lateral segmentectomy[e]	24.1	1.36	54
13	OTCD	Father	44	Left hepatectomy[c]	33.2	0.94	51
19	Methylmalonic academia	Father	37	Left lateral segmentectomy[e]	24.1	3.97	115
20	Methylmalonic acidemia	Father	46	Left hepatectomy[c]	23.6	1.01	66
21	FAP	Brother	66	Left hepatectomy[c]	43.5	0.99	58

[a] Calculated by: [{actual graft weight (g)}/{total liver volume calculated from preoperative CT volumetry (ml)}] × 100%.
[b] Graft-to-recipient weight ratio calculated by [{actual graft weight (g)/ {recipient's body weight (g)}]× 100%.
[c] Resection of segments II + III + IV according to Couinaud's nomenclature for liver segmentation.
[d] Resection of segments V + VI + VII + VIII.
[e] Resection of segments II + III.
OTCD, ornithine transcarbamylase deficiency; FAP, familial amyloid polyneuropathy.

cally available. Furthermore, hepatocyte transplantation could be an alternative to hepatic retransplantation when the graft liver is severely damaged; however, clinical success with these therapies has not yet been reported and probably will not be popularized in the near future (*22,30,31*). Furthermore, the postoperative course of APOLT patients tends to be complicated, as shown in Cases 1, 2, 9, and 10. Until gene therapy or hepatocyte transplantation for these disorders has been established, application of APOLT should be limited to particular cases, such as cases with small-for-size graft (*29*), or cases in which right liver donation threatens donor safety because of an extreme volume imbalance between the right and left hepatic lobes (*32*).

In conclusion, LDLT provides acceptable survival outcomes and excellent quality of life for NCIMLD patients even in cases of a heterozygous carrier donor. The results of the present study suggest that the use of a heterozygous carrier as a liver donor has no negative impact on either the donors or the recipients in LDLT for NCIMLD. However, to confirm our results, enzymatic and genetic assays, using liver tissue extracted from both donor and recipient pairs of LDLT with the use of heterozygotes as donors for these inborn errors of metabolism, should hereafter be mandatory and the remainder of the liver tissue must be preserved for more advanced analyses in the future.

REFERENCES

1. Shneider BL. Pediatric liver transplantation in metabolic disease: Clinical decision making. *Pediatr Transplant* 2002; 6: 25.
2. Leonard JV, McKiernan PJ. The role of liver transplantation in urea cycle disorders. *Molecul Genet and Metabol* 2004; 81: S74.
3. Malago M, Burdelski M, Broelsch CE. Present and future challenges in living related liver transplantation. *Transplant Proc* 1999; 31: 1777.
4. Lacaille F, Sokal E. Living-related liver transplantation. *J Pediatr Gastroentrol Nutr* 2001; 33: 431.
5. Braegger C, Florman S, Shneider B. Living-related liver transplantation in inherited metabolic liver disease: Feasibility and cautions. *J Pediatr Gastroenterol Nutr* 2001; 33: 520.
6. Kasahara M, Ohwada S, Takeichi T, et al. Living-related liver transplantation for type II citrullinemia using a graft from heterozygote donor. *Transplantation* 2001; 71: 157.
7. Ban K, Sugiyama N, Wada Y, et al. A pediatric patient with classic citrullinemia who underwent living-related partial liver transplantation. *Transplantation* 2001; 71: 1495.
8. Endres W. Inherited metabolic diseases affecting the carrier. *J Inher Metab Dis* 1997; 20: 9.
9. Kasahara M, Kiuchi T, Uryuhara K, et al. Treatment of ornithine transcarbamylase deficiency in girls by auxiliary liver transplantation: conceptual changes in living-donor program. *J Pediatr Surg* 1998; 33: 1753.
10. Yorifuji T, Muroi J, Uematsu A, et al. Living-related liver transplantation for neonatal-onset propionic acidemia. *J Pediatr* 2000; 137: 572–574.
11. Kasahara M, Takada Y, Kozaki K, et al. Functional portal flow competition after auxiliary partial orthotopic living donor liver transplantation in noncirrhotic metabolic liver disease. *J Pediatr Surg* 2004; 39: 1138.
12. Terpstra OT. Auxiliary liver grafting: a new concept in liver transplantation. *Lancet* 1993; 342: 758.
13. Whitington PF, Edmond JC, Heffron T, Thistlethwaite JR. Orthotopic auxiliary liver transplantation for Crigler-Najjar syndrome type I. *Lancet* 1993; 342: 779.
14. Ikegami T, Shiotani S, Ninomiya M, et al. Auxiliary partial orthotopic liver transplantation from living donors. *Surgery* 2002; 131: S205.
15. Morimoto T, Ichiyama M, Tanaka A, et al. Guidelines for donor selection and an overview of the donor operation in living related liver transplantation. *Transpl Int* 1996; 9: 208.
16. Fujita S, Kim ID, Uryuhara K, et al. Hepatic grafts from live donors: donor morbidities for 470 cases of liver donation. *Transpl Int* 2000; 13: 333.

17. Saudubray JM, Touati G, Delonlay P, et al. Liver transplantation in propionic acidemia. *Eur J Pediatr*; 158: S65-S69.
18. Jansen PLM. Diagnosis and management of Crigler-Najjar syndrome. *Eur J Pediatr* 1999; 158: S89.
19. Hoff WV, McKiernan PJ, Surtees RAH, Leonard JV. Liver transplantation for methylmalonic acidemia. *Eur J Pediatr* 1999; 158: S70.
20. Michel SJ, Given II CA, Robertson Jr. WC. Imaging of the brain including diffusion-weighted imaging in methylmalonic acidemia. *Pediatr Radiol* 2004; 34: 580.
21. Adams D. Hereditary and acquired amyloid neuropathies. *J Neurol* 2001; 647-657.
22. Horslen SP, McCowan TC, Goertzen TC, et al. Isolated hepatocyte transplantation in an infant with a severe urea cycle disorder. *Pediatrics* 2003; 111: 1262.
23. Chakrapani A, Sivakumar P, McKiernan PJ, Leonard VJ. Metabolic stroke in methylmalonic acidemia five years after liver transplantation. *J Pediatr* 2002; 140: 261.
24. Asonuma K, Inomata Y, Kasahara M, et al. Living related liver transplantation from heterozygote genetic carriers to children with Wilson's disease. *Pediatr Transplant* 1999; 3: 201.
25. Online Mendelian Inheritance in Man. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM. Accessed May 31, 2005.
26. Kobayashi K, Sinasac DS, Iijima M, et al. The gene mutated in adult-onset type II citrullinemia encodes a putative mitochondrial carrier protein. *Nat Genet* 1999; 22: 159.
27. Hauser ER, Finkelstein JE, Valle D, Brusilow SW. Allopurinol-induced orotiduria. A test for mutaions at the ornithine carbamoyltransferase locus in women. *N Eng J Med* 1990; 322: 1641.
28. Arranz JA, Riudor E, Rodes M, et al. Optimization of allopurinol challenge: Sample purification, protein intake control, and the use of orotidine response as a discriminative variable improve performance of the test for diagnosing ornithine carbamoyltransferase deficiency. *Clin Chem* 1999; 45: 995.
29. Inomata Y, Kiuchi T, Kim I, et al. Auxiliary partial orthotopic living donor liver transplantation as an aid for small-for-size grafts in larger recipients. *Transplantation* 1999; 67: 1314.
30. Kren BT, Chowdhury NR, Chowdhury JR, Steer CJ. Gene therapy as an alternative to liver transplantation. *Liver Transplant* 2002; 8: 1089.
31. Ohashi K, Park F, Kay MA. Hepatocyte transplantation: clinical and experimental application. *J Mol Med* 2001; 79: 617.
32. Inomata Y, Uemoto S, Asonuma K, Egawa H. Right lobe graft in living donor liver transplantation. *Transplantation* 2000; 69: 258–264.
33. Ikegami T, Kawasaki S, Ohno Y, et al. Temporary auxiliary liver transplantation from a living donor to an adult recipient with familial amyloid polyneuropathy. *Transplantation* 2002; 73: 628.
34. Jaffe R. Liver transplant pathology in pediatric metabolic disorders. *Pediatr Development Pathol* 1998; 1: 102.
35. Saheki T, Kobayashi K. Mitochondrial aspartate glutamate carrier (citrin) deficiency as the cause of adult-onset type II citrullinemia (CTLN2) and idiopathic neonatal hepatitis (NICCD). *J Hum Genet* 2002; 47: 333.
36. Plochl W, Spiss CK, Plochl E. Death after transplantation of a liver from a donor with unrecognized ornithine transcarbamylase deficiency. *N Engl J Med* 1999; 341: 921.

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.

Mureo Kasahara
Hiroto Egawa
Koichi Tanaka
Organ Transplant Unit
Kyoto University Hospital
Kyoto, Japan

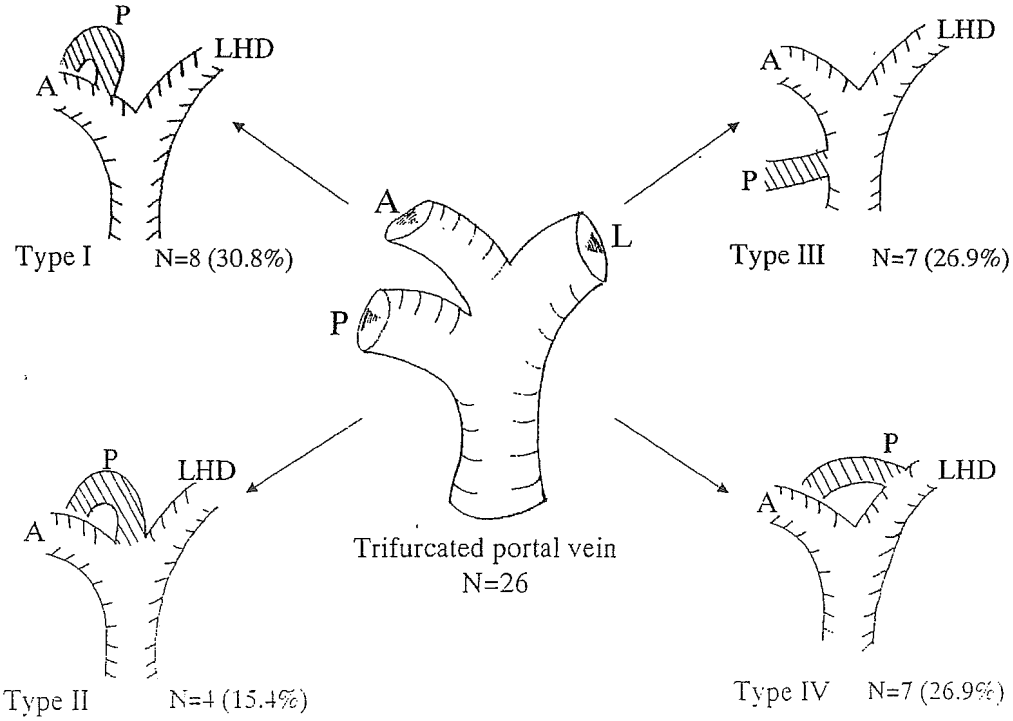

FIGURE 1. Anatomic types of biliary tree in trifurcated portal vein in right-lobe graft defined by tributary from the posterior segment. A, anterior; P, posterior; L, left portal vein; LHD, left hepatic duct.

Kohei Ogawa
Kenji Uryuhara
Yasuhiro Fujimoto
Yasuhiro Ogura
Mikiko Ueda
Yasutsugu Takada
Koichi Tanaka
Department of Transplantation and Immunology
Kyoto University Faculty of Medicine
Kyoto, Japan

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Address correspondence to: Mureo Kasahara, M.D., Department of Transplant Surgery, Kyoto University Hospital, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606–8507, Japan. E-mail: mureo@kuhp.kyoto-u.ac.jp.

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REFERENCES

1. Tanaka K, Kobayashi Y, Kiuchi T. Current status of living donor liver transplantation in adults. *Curr Opin Organ Transplantation* 2000; 5: 74.
2. Delattre JF, Avisse C, Flament JB. Anatomic basis of hepatic surgery. *Surg Clin North Am* 2000; 80: 345.
3. Nakamura T, Tanaka K, Kiuchi T, et al. Anatomical variations and surgical strategies in right lobe living donor liver transplantation: lessons from 120 cases. *Transplantation* 2002; 73: 1896.
4. Ishiko T, Egawa H, Kasahara M, et al. Duct-to-duct biliary reconstruction in living donor liver transplantation utilizing right lobe graft. *Ann Surg* 2002; 236: 235.

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

Daisuke Morioka,[1,2] Mureo Kasahara,[1] Yasutsugu Takada,[3] Yasumasa Shirouzu,[1] Kaoru Taira,[1] Seisuke Sakamoto,[1] Kenji Uryuhara,[1] Hiroto Egawa,[1] Hiroshi Shimada,[2] and Koichi Tanaka[3]

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.

From the [1]Organ Transplant Unit, Kyoto University Hospital, Kyoto, Japan; [2]Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama, Japan; and [3]Department of Transplantation and Immunology, Kyoto University Faculty of Medicine, Kyoto, Japan.

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Address reprint requests to Daisuke Morioka, MD, PhD, Organ Transplant Unit, Kyoto University Hospital, 54, Shogoin-Kawara-cho, Sakyo-ku, Kyoto 606-8507, Japan. Telephone: 81-75-751-3660; FAX: 81-75-751-3616; E-mail: dmorioka@hotmail.com

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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.

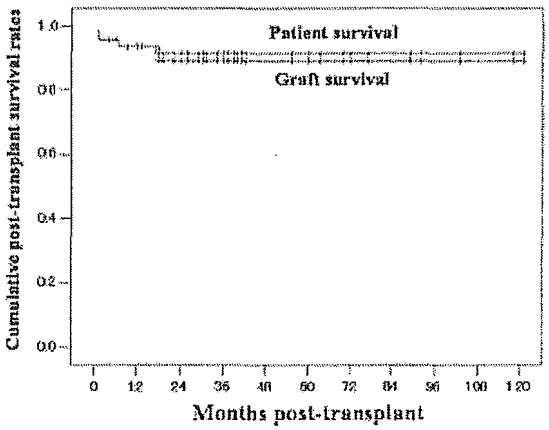

Figure 1. Cumulative posttransplant patient and graft survival rates in 51 patients with urea cycle disorders undergoing liver transplantation. Based on the present analysis, the cumulative posttransplant graft and patient survival rates were 93.7% and 93.7% at 1 year and 88.9% and 91.3% at both 5 and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

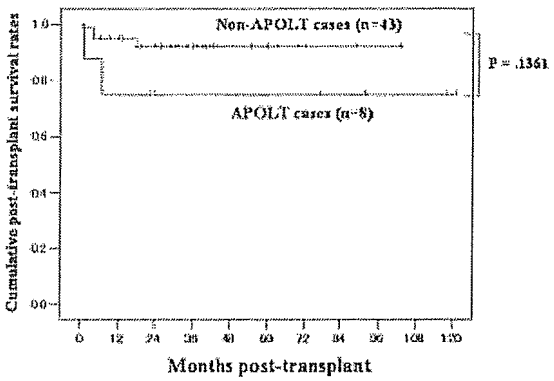

Figure 2. Comparison of cumulative posttransplant patient survival rates between auxiliary partial orthotopic liver transplantation (APOLT) cases and non-APOLT cases. The comparison of posttransplant patient survival between the 8 APOLT cases and the other 43 non-APOLT cases showed that the cumulative 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

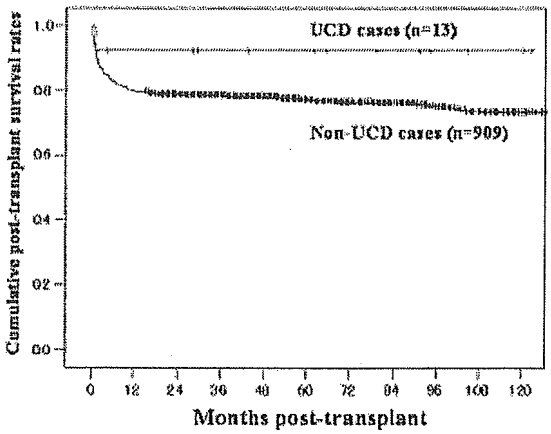

Figure 3. Cumulative posttransplant patient survival rates of 13 patients who underwent living donor liver transplantation (LDLT) and 909 patients who underwent LDLT for other indications during the same study period at Kyoto University. The comparison of cumulative posttransplant patient survival rates 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 hepatectomy.[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.

References

1. Bachmann C. Inherited hyperammonemia. In: Blau et al., eds. Physicians Guide to the Laboratory Diagnosis of Metabolic Diseases. 2nd ed. Berlin: Springer, 2003:261-276.
2. Online Mendelian Inheritance in Man. #311250, Ornithine transcarbamylase deficiency; #237300, Carbamoyl phosphate synthetase deficiency; #207800, Argininemia; #207900, Argininosuccinicaciduria; #215700, Citrullinemia, classic; #603471, Citrullinemia, Type II, Adult-onset; CTLN2; #237310, N-acetyl glutamate synthetase deficiency. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

3. Leonard JV, McKiernan PJ. The role of liver transplantation in urea cycle disorders. Molecul Genet Metabol 2004;81:S74-S78.
4. Whitington PF, Alonso EM, Boyle JT, Molleston JP, Rosenthal P, Emond JC, Millis JM. Liver transplantation for the treatment of urea cycle disorders. J Inherit Metab Dis 1998;21(Suppl 1):S112-S118.
5. Largilliere C, Houssin D, Gottrand F, Mathey C, Checoury A, Alagille D, et al. Liver transplantation for ornithine transcarbamylase deficiency in a girl. J Pediatr 1989:115:415-417.
6. Tuchman M. Persistent acitrullinemia after liver transplantation for carbamylphosphate synthetase deficiency. N Engl J Med 1989;320:1498-1499.
7. Broelsch CE, Emond JC, Whitington PF, Thistlethwaite JR, Baker AL, Lichtor JL. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. Ann Surg 1990;212:368-375.
8. Todo S, Starzle TE, Tzakis A, Benkov KJ, Kalousek F, Saheki T, et al. Orthotopic liver transplantation for urea cycle enzyme deficiency. Hepatology 1992;15:419-422.
9. Jan D, Poggi F, Jouvet P, Rabier D, Laurent J, Beringer A, et al. Definitive cure of hyperammonemia by liver transplantation in urea cycle defects: report of three cases. Transplant Proc 1994; 26:188.
10. Hasegawa T, Tzaksi AG, Todo S, Reyes J, Nour B, Finegold DN, et al. Orthotopic liver transplantation for ornithine transcarbamylase deficiency with hyperammonemic encephalopathy. J Pediatr Surg 1995;30:863-865.
11. Kawamoto S, Strong RW, Kerlin P, Lynch SV, Steadman K, Nakagawa S, et al. Orthotopic liver transplantation for adult-onset type II citrullinemia. Clin Transpl 1997;11:453-458.
12. Busuttil AA, Goss JA, Seu P, Dulkanchainun TS, Yanni GS, McDiarmid SV, Busuttil RW. The role of orthotopic liver transplantation in the treatment of ornithine transcarbamylase deficiency. Liver Transpl Surg 1998;4:350-354.
13. Fletcher JM, Couper R, Moore D, Coxon R, Dorney S. Liver transplantation for citrullinemia improves intellectual function. J Inherit Metab Dis 1999;22:581-586.
14. Takenaka K, Yasuda I, Araki H, Fukutomi Y, Ohnishi H, Yamakita N, et al. Type II citrullinemia in an elderly patient treated with living related partial liver transplantation. Intern Med 2000;39:553-558.
15. Kasahara M, Ohwada S, Takeichi T, Kaneko H, Tomomasa T, Morikawa A, et al. Living-related liver transplantation for type II citrullinemia using a graft from heterozygote donor. Transplantation 2001;71:157-159.
16. Ban K, Sugiyama N, Sugiyama K, Wada Y, Suzuki T, Hashimoto T, et al. A pediatric patient with classical citrullinemia who underwent living-related partial liver transplantation. Transplantation 2001;71:1495-1497.
17. Santos Silva E, Martins E, Cardoso ML, Barbot C, Vilarinho L, Medina M. Liver transplantation in a case of argininaemia. J Inherit Metab Dis 2001;24:885-887.
18. Ikeda S, Yazaki M, Takei Y, Ikegami T, Hashikura Y, Kawasaki S, et al. Type II (adult onset) citrullinemia: clinical pictures and the therapeutic effect of liver transplantation. J Neurol Neurosurg Psychiatry 2001;71:663-670.
19. Tamamori A, Okano Y, Ozaki H, Fujimoto A, Kajiwara M, Fukuda K, et al. Neonatal intrahepatic cholestasis caused by citrin deficiency: severe hepatic dysfunction in an infant requiring liver transplantation. Eur J Pediatr 2002;161:609-613.
20. Yazaki M, Hashikura Y, Takei Y, Ikegami T, Miyagawa S, Yamamoto K, et al. Feasibility of auxiliary partial orthotopic liver transplantation from living donors for patients with adult-onset type II citrullinemia. Liver Transpl 2004;10:550-554.
21. McBride KL, Miller G, Carter S, Karpen S, Goss J, Lee B. Developmental outcomes with early orthotopic liver transplantation for infants with neonatal-onset ornithine transcarbamylase deficiency. Pediatrics 2004;114:523-526.
22. Uemoto S, Yabe S, Inomata Y, Nishizawa H, Asonuma K, Tanaka K, et al. Coexistence of a graft with the preserved native liver in auxiliary partial orthotopic liver transplantation from a living donor for ornithine transcarbamylase deficiency. Transplantation 1997;63:1026-1028.
23. Kasahara M, Kiuchi T, Uryuhara K, Ogura Y, Takakura K, Tanaka K, et al. Treatment of ornithine transcarbamylase deficiency in girls by auxiliary liver transplantation: conceptual changes in a living-donor program. J Pediatr Surg 1998;33: 1753-1756.
24. Kasahara M, Takada Y, Kozaki K, Uryuhara K, Ogura Y, Tanaka K, et al. Functional portal flow competition after auxiliary partial orthotopic living donor liver transplantation in noncirrhotic metabolic liver disease. J Pediatr Surg 2004; 39:1138-1141.
25. Hauser ER, Finkelstein JE, Valle D, Brusilow SW. Allopurinol-induced orotiduria. A test for mutations at the ornithine carbamoyltransferase locus in women. N Engl J Med 1990;322: 1641-1645.
26. Arranz JA, Riudor E, Rodes M, Roig M, Climent C, Rubio V, et al. Optimization of allopurinol challenge: sample purification, protein intake control, and the use of orotidine response as a discriminative variable improve performance of the test for diagnosing ornithine carbamoyltransferase deficiency. Clin Chem 1999;45:995-1001.
27. Morimoto T, Ichiyama M, Tanaka A, Ikai I, Yamamoto Y, Nakamura Y, et al. Guidelines for donor selection and an overview of the donor operation in living related liver transplantation. Transpl Int 1996;9:208-213.
28. Fujita S, Kim ID, Uryuhara K, Asonuma K, Egawa H, Kiuchi T, et al. Hepatic grafts from live donors: donor morbidities for 470 cases of liver donation. Transpl Int 2000;13:333-339.
29. Kobayashi K, Sinasac DS, Iijima M, Boright AP, Begum L, Lee JR, et al. The gene mutated in adult-onset type II citrullinemia encodes a putative mitochondrial carrier protein. Nat Genet 1999;22:159-163.
30. Keeffe EB. Selection of patients for liver transplantation. In: Maddrey WC, et al., eds. Transplantation of the Liver. 3rd ed. Philadelphia: Lippincott Williams and Wilkins, 2001:5-34.
31. Belanger-Quintana A, Martinez-Pardo M, Garcia MJ, Wermuth B, Torres J, Pallares E, Ugarte M. Hyperammonaemia as a cause of psychosis in an adolescent. Eur J Pediatr 2003;162:773-775.
32. Kasahara M, Kaihara S, Oike F, Ito T, Fujimoto Y, Tanaka K, et al. Living-donor liver transplantation with monosegments. Transplantation 2003;76:694-696.
33. Sugawara Y, Makuuchi M. Advances in adult living donor liver transplantation: a review based on reports from the 10th anniversary of the adult-to-adult living donor liver transplantation meeting in Tokyo. Liver Transpl 2004;10:715-720.
34. Kiuchi T, Tanaka K, Ito T, Oike F, Ogura Y, Tanaka K, et al. Small-for-size graft in living donor liver transplantation: how far should we go? Liver Transpl 2003;9(Suppl 9): S29-S35.
35. Ito T, Kiuchi T, Egawa H, Kaihara S, Oike F, Tanaka K, et al. Surgery-related morbidity in living donors of right-lobe liver

graft: lessons from the first 200 cases. Transplantation 2003;76: 158-163.
36. Akabayashi A, Slingsby BT, Fujita M. The first donor death after living-related liver transplantation in Japan. Transplantation 2004;77:634.
37. Kren BT, Chowdhury NR, Chowdhury JR, Steer CJ. Gene therapy as an alternative to liver transplantation. Liver Transpl 2002;8:1089-1108.
38. Ohashi K, Park F, Kay MA. Hepatocyte transplantation: clinical and experimental application. J Mol Med 2001;79:617-630.
39. Kasahara M, Takada Y, Egawa H, Fujimoto Y, Ogura Y, Ogawa K, et al. Auxiliary partial orthotopic living donor liver transplantation: Kyoto University experience. Am J Transplant 2005;5: 558-565.
40. Plochl W, Spiss CK, Plochl E. Death after transplantation of a liver from a donor with unrecognized ornithine transcarbamylase deficiency. N Engl J Med 1999;341:921-922.
41. Yorifuji T, Muroi J, Uematsu A, Tanaka K, Kiwaki K, Endo F, et al. X-inactivation pattern in the liver of a manifesting female with ornithine transcarbamylase (OTC) deficiency. Clin Genet 1998; 54:349-353.
42. McDiarmid SV, Merion RM, Dykstra DM, Harper AM. Selection of pediatric candidates under the PELD system. Liver Transpl 2004;10(Suppl 2):S23-S30.

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

Kentaro Matsubara,[1,2] Yasuhiro Fujimoto,[1] Hideya Kamei,[1] Kohei Ogawa,[1] Mureo Kasahara,[1] Mikiko Ueda,[1] Hiroto Egawa,[1] Yasutsugu Takada,[1] Masaki Kitajama,[2] and Koichi Tanaka[1]

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.

From the [1]Department of Transplantation and Immunology, Kyoto University Faculty of Medicine, Kyoto, Japan, and the [2]Department of Surgery, Keio University School of Medicine, Tokyo, Japan.

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Address reprint requests to Kentaro Matsubara, MD, Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Telephone: 81-3-3353-1211; FAX: 81-3-3355-4707; E-mail: m-ken@dk9.so-net.ne.jp

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