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Outcomes After Living Donor Liver Transplantation in Pediatric Patients with Inherited Metabolic Diseases

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Yukihiro Sanada
DF Yasunaru Sakuma
B Yasuharu Onishi
B Noriki Okada
B Naoya Yamada
B Yuta Hirata
B Go Miyahara
B Takumi Katano
B Toshio Horiuchi
B Takahiko Omameuda
DF Alan Kawarai Lefor
DF Naohiro Sata

Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Shimotsuke, Toichigi, Japan

Corresponding Author: Yukihiro Sanada, e-mail: yuki371@jichi.ac.jp
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Background: There is no consensus about the long-term prognosis of pediatric patients with a variety of rare liver diseases but with inherited metabolic diseases (IMDs). We retrospectively reviewed the developmental outcomes of patients with IMDs undergoing living donor liver transplantation (LDLT).

Material/Methods: Between May 2001 and December 2020, of 314 pediatric patients who underwent LDLT, 44 (14%) had IMDs. The median age at LDLT was 3.0 years old (range 0-15.0 years). Associations between the post-transplant complications and graft survival rate in patients with IMDs and biliary atresia (BA) were calculated. We evaluated the safety of LDLT from heterozygous carrier donors, the prognosis of patients with IMDs who have metabolic defects expressed in other organs, and developmental outcomes of patients with IMDs.

Results: The 10-year graft survival rates in patients with IMDs and BA were 87% and 94%, respectively (P=0.041), and the causes of graft failure included pneumocystis pneumonia, acute lung failure, hemophagocytic syndrome, hepatic vein thrombosis, portal vein thrombosis, and sepsis. The rate of post-transplant cytomegalovirus viremia in patients with IMDs was higher than that of patients with BA (P=0.039). Of 39 patients with IMDs, 15 patients (38%) had severe motor and intellectual disabilities in 4 patients, intellectual developmental disorders including epilepsy in 2, and attention-deficit hyperactivity disorder in 2. Of 28 patients with IMDs, 13 (46%) needed special education.

Conclusions: The long-term outcomes of LDLT in patients with IMDs are good. However, further long-term social and educational follow-up regarding intellectual developmental disorders is needed.

Keywords: **Brain Diseases, Metabolic, Inborn • Liver Cirrhosis, Biliary • Liver Transplantation**

Abbreviations: **LT** – liver transplantation; **IMD** – inherited metabolic disease; **LDLT** – living donor liver transplantation; **BA** – biliary atresia; **OTCD** – ornithine transcarbamylase deficiency; **MMA** – methylmalonic academia; **POD** – post-operative day; **D** – donor; **R** – recipient; **GV/SLV** – graft volume/standard liver volume ratio; **DDLT** – deceased donor liver transplantation

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/932994

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Background

Liver transplantation (LT) is an established curative treatment for pediatric patients with end-stage liver diseases such as liver cirrhosis. The reported incidence of LT for patients with inherited metabolic diseases (IMDs) is 8.0-20.2% [1-9]. It has been reported that the 5-year and 10-year graft survival rates in patients with IMDs were 73.1-94.5% [1-5,7-9] and 62.0-90.0% [2-4,7,8], respectively. However, there are many problems surrounding LT for patients with IMDs. Although there is a possibility of heterozygous carrier donors in the case of living donor liver transplantation (LDLT) for patients with IMDs, there is no consensus about the safety of LDLT from heterozygous carrier donors [10-13]. Although the prognosis of patients with urea cycle diseases is good because LT is curative, the prognosis of patients with IMDs who have metabolic defects expressed in other organs remains undefined [3,14-18]. In addition, although there are potential intellectual developmental disorders and neurological sequelae in patients with IMDs and hyperammonemia, the outcomes for these patients are unclear.

We present a retrospective analysis of our experience performing LDLT on patients with IMDs, focusing on their long-term prognosis and associated intellectual developmental problems.

Material and Methods

Patients

Between May 2001 and December 2020, 314 LDLTs were performed on pediatric patients with end-stage liver disease, acute liver failure, and IMDs in our institution. Of these, 221 patients with biliary atresia (BA) and 44 patients with IMDs underwent LDLT; these patients were included in this study. Forty-four patients (14%) had IMDs including ornithine transcarbamylase deficiency (OTCD) (n=19), Wilson's disease (n=5), neonatal hemochromatosis (n=5), maple syrup urine disease (n=4), methylmalonic acidemia (MMA) (n=3), progressive familial intrahepatic cholestasis type 1 (n=2), and citrullinemia (n=2), as well as cystic fibrosis, carbamoyl phosphate synthetase 1 deficiency, Niemann-Pick disease type C, and glycogen storage disease type Ia (each n=1). The indications for LT in patients with IMDs were improvement of quality of life of patients with severe disease manifestations or life-threatening metabolic decompensations despite medical and dietary management. The mean observation time between May 2001 and December 2020 was 10.6±5.4 years. Demographic data for recipients and graft information are shown in **Table 1**. Approval to conduct this study was obtained from the university clinical research ethics review board at our university (CU No. 20-001).

Surgical Procedure of LDLT

The type of donor hepatectomy was determined based on the recipient's standard liver volume, recipient's weight, and graft volume by preoperative computed tomographic volumetry [19,20]. The donor's biliary anatomy was evaluated performing intraoperative real-time cholangiography 3 times to define the biliary anatomy, determine the biliary transection line, and identify biliary leakage. A routine donor hepatectomy was performed using intraoperative ultrasonic guidance. The donor's left hilar plate was transected using a scalpel.

For the recipient operation, inverted T-shape incisions were used, and total hepatectomy was performed. In many infants, after total hepatectomy, the recipient's right, middle, and left hepatic veins became a single orifice, and the recipient's hepatic vein was anastomosed to the graft's hepatic vein. The recipient's portal vein was anastomosed to the graft's left portal vein. Hepatic artery reconstruction was performed using microsurgical techniques. Biliary reconstruction was performed using a Roux-en-Y hepaticojejunostomy.

Immunosuppression Therapy

Tacrolimus and methylprednisolone were used as standard postoperative immunosuppression therapy. The target trough level of tacrolimus was gradually decreased. Mycophenolate mofetil was used when more potent immunosuppression was required; for example, in ABO-incompatible recipients, in patients with acute cellular rejection episodes, or in patients with liver dysfunction after the cessation of methylprednisolone therapy.

Post-Transplant Management

During the post-transplant period, patients routinely received anticoagulants and underwent Doppler ultrasonography. Anticoagulation treatment was started with intravenous dalteparin sodium (100 U/kg/day) several days postoperatively. If hepatic inflow and outflow were sufficient, we usually withdrew anticoagulant at post-operative day (POD) 14. Doppler ultrasonography was used for follow-up imaging surveillance. Doppler ultrasonography was performed routinely twice per day until hospital discharge, and thereafter at 1, 3, 5, and 9 months, and then every 6 months after LDLT.

In our department, surveillance for infection is based on peripheral blood studies. Serum cytomegalovirus antigenemia (C7-HRP) and β-D-glucan were performed routinely once per week until hospital discharge, and monthly thereafter following LDLT. Prophylactic treatments due to antiviral and antifungal agents were performed if the serum C7-HRP and β-D-glucan was positive.

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Table 1. Demographic data for recipients and graft information.

Patient	Recipients with IMDs	Recipients with BA	*p*-value
Period	May 2001-December 2020		
Number	44	221	
Gender	Male: 22, Female: 22	Male: 74, Female: 147	0.041
Age (years old)	3.0 (0.0-15.0) years old	1.0 (0.0-16.0) years old	0.076
Weight	14.2 (2.6-64.9) kg	9.2 (4.8-58.5) kg	0.079
Original disease	OTCD: 19, Wilson's disease: 5, Neonatal hemochromatosis: 5, Maple syrup urine disease: 4, MMA: 3, Progressive familial intrahepatic cholestasis type 1: 2, Citrullinemia: 2, Others: 4	–	
ABO-compatibility	Identical/Compatible: 32, Incompatible: 12	Identical/Compatible: 189, Incompatible: 32	0.046
PELD/MELD score	0 (0-29)	11 (0-37)	<0.001
Type of graft	Left lateral segment: 20, Left lobe: 12, Segment 2 monosegment: 6, Left lobe + caudate lobe: 3, Reduced left lateral segment: 2, Segment 3 monosegment: 1	Left lateral segment: 156, Left lobe: 41, Reduced left lateral segment: 13, Left lobe+caudate lobe: 7, Segment 2 monosegment: 3, Posterior segment: 1	
GV/SLV	65.7±19.0%	73.7±21.0%	0.012
Operation time	864 min±260 min	870 min±280 min	0.843
Cold ischemic time	111 min±59 min	141 min±1 hr 51 min	0.204
Warm ischemic time	50 min±19 min	51 min±18 min	0.451
Bleeding volume	79.3±117.7 ml/kg	101.4±98.8 ml/kg	0.002
Transfusion volume	133.6±202.8 ml/kg	121.4±102.8 ml/kg	0.070
Observation period	10.6±5.4 years		

IMDs – inherited metabolic diseases; BA – biliary atresia; OTCD – ornithine transcarbamylase deficiency; MMA – methylmalonic academia; PELD – pediatric end-stage liver disease; MELD – model for end-stage liver disease; GV/SLV – graft volume/standard liver volume ratio.

Statistical Analysis

The significance of differences between 2 groups was evaluated using the chi-squared test and Mann-Whitney U test. Associations between the recipient, graft, and post-transplant complications were evaluated using univariate analysis. Graft survival rates were calculated by the Kaplan-Meier product-limited method, and differences in survival between the 2 groups were then compared using the log-rank test. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), and differences were considered to be significant with values of $P<0.05$.

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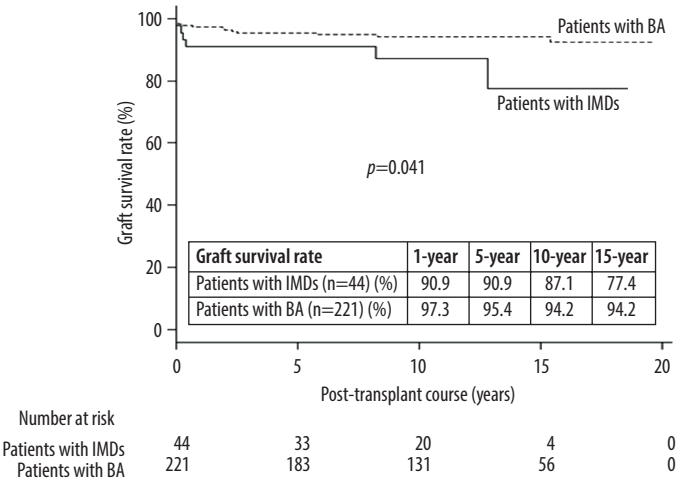

Graft survival rate	1-year	5-year	10-year	15-year
Patients with IMDs (n=44) (%)	90.9	90.9	87.1	77.4
Patients with BA (n=221) (%)	97.3	95.4	94.2	94.2

Figure 1. Graft survival rates in patients with IMDs and BA. IMDs – inherited metabolic disease, BA – biliary atresia.

Results

Graft Survival Rates

The 10-year graft survival rates in patients with IMDs and BA were 87% and 94%, respectively (*P*=0.041) (**Figure 1**). The causes of graft failure included pneumocystis pneumonia, acute lung failure, hemophagocytic syndrome, hepatic vein thrombosis, portal vein thrombosis, and sepsis in patients with IMDs. Of the patients with graft failure, 2 patients underwent repeat LT. One patient with graft failure due to hepatic vein thrombosis underwent deceased donor liver transplantation 8.2 years after the first LDLT and did well. Another patient with graft failure due to portal vein thrombosis underwent repeat LDLT on POD 15 and died of sepsis. The causes of graft failure included chronic rejection in 5 patients with BA, bowel perforation in 2, bowel perforation in 2, acute encephalitis in 2, cerebral hemorrhage in 1, hepatic vein thrombosis in 1, veno-occlusive disease in 1, and sepsis in 1. Of the 7 patients with graft failure due to chronic rejection, hepatic vein thrombosis, and veno-occlusive disease, all patients underwent repeat LT.

Analysis of Risk Factors for Post-Transplant Complications in Patients with IMDs and BA

The rate of post-transplant acute cellular rejection in patients with IMDs was lower than that with BA (27% vs 44%, *P*=0.044) (**Table 2**). The rate of post-transplant cytomegalovirus viremia in patients with IMDs was higher than that with BA (50% vs 33%, *P*=0.039) (**Table 2**). Serological patterns of cytomegalovirus infection in patients with IMDs (n=43) were Donor (D)+/Recipient (R)+ in 17 patients, D+/R– in 12, D–R+ in 6, and D–R– in 8. Serological patterns of cytomegalovirus infection in patients with BA (n=219) were D+/R+ in 111 patients, D+/R– in 51, D–R+ in 20, and D–R– in 37.

LDLT for Patients with OTCD Using a Graft from a Heterozygous Carrier Donor

Relationships between donor and recipient in patients with OTCD (n=19) were father in 12 patients, mother without heterozygous carrier in 5, mother with heterozygous carrier in 1, and maternal aunt without heterozygous carrier in 1. One male patient with OTCD had indications for LT because his disease was the neonatal-onset type (day8, NH_3 901 μmol/L) and was resistant to medical treatment at 3 years of age (**Table 3**, OTCD Case 5) [13]. Except for the OTCD carrier mother, there were no voluntary donor candidates. His mother was doing well and never had any symptoms suggesting hyperammonemia. In addition, her serum ammonia level was normal, and the OTC activity in her liver was 104.4%. He underwent LDLT using a left lateral segment graft from a heterozygous carrier donor at 3.4 years old. The graft volume was 244 g. The donor's remnant liver volume 81.8%, and graft volume/standard liver volume ratio (GV/SLV) was 54.0%. The post-transplant clinical course was uneventful and they are both doing well without intellectual developmental disorders at 11.4 years after LDLT.

Long-Term Outcomes of LDLT in Patients with IMDs who Have Metabolic Defects Expressed in Other Organs

Our experience with LDLT for patients with methylmalonic acidemia is shown in **Table 4**. Three patients with methylmalonic acidemia have normal renal function with restricted diets, but the long-term renal prognosis is not clear. Two patients have growth and developmental disorders, but 1 patient who underwent LDLT at 2 months old has no growth or developmental disorders. One female patient with acute liver failure underwent LDLT using a segment 2 mono-segment graft from her father at 59 days of age. She had progressive neurologic dysfunction and required long-term ventilatory support with

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Table 2. Univariate analysis of risk factors for post-transplant complications in recipients with IMDs and BA.

Variable	Recipients with IMDs N=44	Recipients with BA N=221	*p*-value
Hepatic vein complications	2 (4.5%)	15 (6.8%)	0.746
Portal vein complications	4 (9.1%)	38 (17.2%)	0.257
Hepatic artery complications	2 (4.5%)	11 (5.0%)	0.999
Biliary complications	8 (18.2%)	45 (20.4%)	0.839
Re-laparotomy after LDLT	7 (15.9%)	22 (10.0%)	0.288
Acute cellular rejection	12 (27.3%)	98 (44.3%)	0.044
Steroid-resistant acute rejection	1 (2.3%)	26 (11.8%)	0.059
Cytomegalovirus viremia	22 (50.0%)	73 (33.0%)	0.039
Post-transplant lymphoproliferative disorder	0 (0%)	6 (2.7%)	0.594
Hospital length of stay	62±107 days	43±30 days	0.125

IMDs – inherited metabolic diseases; BA – biliary atresia; LDLT – living donor liver transplantation.

Table 3. Outcomes of LDLT using grafts from OTCD heterozygous carrier donors.

Number	OTCD Case 1	OTCD Case 2	OTCD Case 3	OTCD Case 4	OTCD Case 5
Institutions	Nagasaka H [9] (2001)	Mukhtar A [10] (2013)	Rahayatri TH [11] (2016)	Rahayatri TH [11] (2016)	Our patient [12] (2012)
Recipient age/gender	4.8 y/Female	42 y/Male	5 y/Female	5 y/Female	3.3 y/Male
Recipient OTC activity of liver	13%	–	15%	9.7%	0%
Donor age/gender relationship/symptom	35 y/Female Mother/None	36 y/Female Sister/None	34 y/Female Mother/None	38 y/Female Mother/None	32 y/Female Mother/None
Donor allopurinol loading test	Orotic acid(urine) (35.62µmol/L)	–	–	–	Orotic acid(urine) (22.75 µmol/L)
Graft OTC activity of liver	49%	–	62%	42.6%	104.4%
Graft	LLS GV: 252 g RLV: 79.8%	RL GRWR: 0.9% RLV: 40%	LLS	LLS	LLS GV/SLV: 54.0% RLV: 81.8%
Recipient post-transplant course	Uneventful	POD2: NH3 762 POD5: death	POD1: NH3 338 CVVHD (4 days) Medication (phenylbutyrate)	POD2: NH3 430 CVVHD (3 days) No medication	Uneventful
Donor post-transplant course	Uneventful	POD3: NH3 280 POD12: discharge	Uneventful	Uneventful	Uneventful

OTCD – ornithine transcarbamylase deficiency; y – years old; LLS – left lateral segment; RL – right lobe; GV – graft volume; GRWR – graft-to-recipient weight ratio; GV/SLV – graft volume/standard liver volume ratio; RLV – remnant liver volume; POD – post-operative day;0 CVVHD – continuous veno-venous hemodialysis.

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Table 4. Outcomes of LDLT for patients with MMA in our institution.

Number	MMA Case 1	MMA Case 2	MMA Case 3
Recipient gestational age/BW/gender	38 w/2860 g/Male	36 w/2632 g/Female	39 w/2576 g/Male
Onset/symptom	Day3/Suckling defect (pH 7.320, NH3 613)	Day22/Abnormal screening test (pH 7.180, NH3 232)	Day20/Abnormal screening test (pH 7.416, NH3 125)
Disease type	mut^0	mut^0	mut^0
Treatment	Protein-restricted diet (1.5 g/kg/day) levocarnitine, vitamins	Protein-restricted diet (2.0 g/kg/day) levocarnitine, vitamins	Protein-restricted diet (2.7 g/kg/day) levocarnitine, vitamins
Developmental disorder before LDLT	DQ 70	–	DQ 78
Recipient age at LDLT	10 months old	2 months old	9 months old
Post-transplant complications	Portal vein stenosis Cytomegalovirus infection	Hepatic vein stenosis Cytomegalovirus infection	None
Post-transplant protein-restricted diet	Severe fussy eater	Protein-restricted diet (30 g/day)	Concomitant use of protein-restricted milk
Medications at present	Tac levocarnitine, vitamins (6.1POY)	Tac levocarnitine, vitamins (3.8POY)	Tac, mPSL, MMF levocarnitine, vitamins (3.7POY)
Growth disorder at present	BH: 113.5 cm (-2.3 SD) BW: 23.3 kg (-0.6S D)	BH: 98.0 cm (-0.9 SD) BW: 15.9 kg (0.0 SD)	BH: 96.2 cm (-2.2 SD) BW: 14.2 kg (-1.3 SD)
Developmental disorder at present	Special needs education	None	Attention-deficit hyperactivity disorder
Renal function at present	eGFR 77 ml/min/1.73 m^2	eGFR 110 ml/min/1.73 m^2	eGFR 96 ml/min/1.73 m^2

MMA – methylmalonic academia; BW – body weight; w – week of gestational age; LDLT – living donor liver transplantation; DQ – development quotient; Tac – tacrolimus; mPSL – methylprednisolone; MMF – mycophenolate mofetil; POY – post-operative year; BH – body height; SD – standard deviation; eGFR – estimated glomerular filtration rate.

a tracheostomy and nutrition via gastrostomy. The period of diagnosis of Niemann-Pick disease type C was 1.6 years after LDLT. She has progressive neurologic dysfunction, Niemann-Pick disease type C cell infiltration of the graft liver, and secondary Crohn's disease at present [21]. One patient with cystic fibrosis died of progressive respiratory failure 12 years after LDLT.

Outcomes of younger siblings after LDLT in patients with IMDs

Eleven patients with IMDs who had younger siblings after LDLT included patients with neonatal hemochromatosis (n=4), OTCD (n=3), progressive familial intrahepatic cholestasis type 1 (n=1), carbamoyl phosphate synthetase 1 deficiency (n=1), MMA (n=1), and Niemann-Pick disease type C (n=1). Of the younger siblings of 4 patients with neonatal hemochromatosis, 2 underwent antenatal maternal high-dose immunoglobulin treatment to prevent neonatal hemochromatosis [22]. However, 1 child without immunoglobulin treatment who underwent LDLT from the puerperal mother developed neonatal hemochromatosis and another did not develop neonatal hemochromatosis. In younger siblings of patients with OTCD, 1 carrier received medical treatment and 1 neonate with OTCD underwent DDLT. In younger siblings of patients with carbamoyl phosphate synthetase 1 deficiency, MMA, and Niemann-Pick disease type C, 3 had prenatal amniotic fluid analysis and were healthy.

Current State of Intellectual Developmental Disorders in Patients with IMDs

Of 39 patients with IMDs (excluding 5 patients who have died), 15 patients (38%) had severe motor and intellectual disabilities in 4 patients, intellectual developmental disorders including epilepsy in 2, and attention-deficit hyperactivity disorder in 2. Of 28 patients with IMDs (excluding 6 workers and 5 preschool patients), 13 (46%) needed special education.

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Table 5. Post-transplant survival rates of patients with IMDs.

Institutions	Number of patients	Survival	Complications or others
McKiernan PJ (2019) [1] SRTR	2354 (17%)	5-year graft: 94.5%	* Survival rates of IMDs patients with extrahepatic disease were low * Survival improved with younger age at LT until age <2 years
Kim JS (2015) [2] Asan Medical Center	54 (1.6%)	1-year graft: 88.8% 5-year graft: 85.5% 10-year graft: 85.5%	* Survival rates between LDLT and DDLT were same * Recurrence of IMDs was none
Mazariegos G (2014) [3] Children's Hospital of Pittsburgh	285	1-year graft: 79.3% 5-year graft: 73.1% 10-year graft: 67.4% 20-year graft: 56.9%	* Survival rate after 2000 was 97% * Survival rates of UCDs and MSUD were high
Kasahara M (2014) [4] Japan registry	194 (8.7%)	1-year graft: 91.2% 5-year graft: 87.9% 10-year graft: 86.1% 15-year graft: 74.4%	* Asymptomatic heterozygous carrier donors were safe * Survival rates of UCDs and Wilson's disease were high
Arnon R (2010) [5] SPLIT registry	446 (14.9%)	1-year graft: 90.8% 5-year graft: 83.8%	* Post-transplant complications rates were low
Stevenson T (2010) [6] Stanford University	54	recipient: 100% (Observation period: 5.4±4.4 year)	* Number of combined liver-kidney transplantation was twelve * Mental and developmental retardations were improved
Sze YK (2009) [7] King's college Hospital	96 (16.7%)	1-year graft: 83% 5-year graft: 77% 10-year graft: 62%	* Survival rates of acute liver failure and less than 1-year-old were low
Morioka D (2005) [8] Kyoto University	46 (8.0%)	1-year recipient: 86.8% 5-year recipient: 81.2% 10-year recipient: 81.2%	* Heterozygous carrier donors were safe * Survival rates of IMDs recipients who have metabolic defects expressed in other organs were low
Kayler LK (2003) [9] UNOS	551 (20.2%)	1-year recipient: 94% 5-year recipient: 92%	* Survival rates of simultaneous transplantation of other organs were low
Our study Jichi Meidcal University	44 (14.0%)	1-year graft: 90.9% 5-year graft: 90.9% 10-year graft: 87.1%	* Morbidity rate of cytomegalovirus viremia was high * Survival rates of IMDs recipients who have metabolic defects expressed in other organs were low

IMDs – inherited metabolic diseases; SRTR – the Scientific Registry of Transplant Recipients; LT – liver transplantation; LDLT – living donor liver transplantation; DDLT – deceased donor liver transplantation; UCD – urea cycle disorders; MSUD – maple syrup urine disease; UNOS; the United Network for Organ Sharing.

Discussion

The reported rate of LT in patients with IMDs is 8.0-20.2% [1-9]. The 5-year and 10-year graft survival rates in patients with IMDs are reportedly 73.1-94.5% [1-5,7-9] and 62.0-90.0% [2-4,7-8], respectively (**Table 5**). Few patients with BA undergo LT and there is a wide variation of outcomes among institutions. In this study, the 10-year graft survival rates in patients with IMDs and BA were 87% and 94%, respectively (P=0.041). The long-term outcomes of LDLT in patients with IMDs were good, and there was no association between graft failure and post-transplant complications. In addition, there were no differences in causes of graft failure between patients with IMDs and BA. The rate of post-transplant cytomegalovirus viremia in patients with IMDs was higher than that with BA (50% vs 33%, P=0.039) despite the low rate for acute cellular rejection (27% vs 44%, P=0.044) (**Table 2**). The rate of cytomegalovirus viremia in patients of D+R– with IMDs and BA were 75% and

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67%, respectively (*P*=0.737). Post-transplant cytomegalovirus viremia occurred in patients with IMDs despite minimal use of steroid-pulse therapy and low risk of serological patterns. We believe that post-transplant cytomegalovirus viremia in patients with IMDs was a pre-transplant abnormal nutritional condition due to a protein-restricted diet.

There are many problems associated with LT for patients with IMDs. The indications for LT in patients with IMDs who have metabolic defects expressed in other organs are to preserve life, prevent life-threatening complications, and improve the quality of life (release from restricted diets and prevention of developmental disorders). However, LT for patients with IMDs who have metabolic defects expressed in other organs is not a curative treatment [3,14-18]. Therefore, adequate informed consent regarding the benefits and risks of LT, including the possibility of poor outcomes after LT, should be obtained in each case. In patients with MMA, continuing metabolic damage to the kidneys and brain may occur even after successful LT [23,24]. It has been reported that LT should be performed as a therapeutic option in the early stages of the disease because LT allows prevention of decompensation episodes, normalization of dietary protein intake, and a marked improvement in quality of life [25]. In this study, the 1 patient who underwent LDLT at 2 months had no growth or developmental disorders (**Table 4**). In patients with Niemann-Pick disease type C, neonatal-onset Niemann-Pick disease type C often presents with jaundice and hepatosplenomegaly from birth, and rarely progresses to liver failure. Therefore, patients with neonatal-onset Niemann-Pick disease type C may require simultaneous diagnosis and treatment [21]. Sufficient informed consent about the chance of post-transplant diagnosis of Niemann-Pick disease type C and poor neurological prognosis should be obtained before LT. We diagnosed Niemann-Pick disease type C 1.6 years after LDLT, and she had progressive neurologic dysfunction requiring long-term ventilatory support with a tracheostomy and nutrition via gastrostomy. She has progressive neurologic dysfunction, Niemann-Pick disease type C cell infiltration of the graft liver, and secondary Crohn's disease at present [21]. Cystic fibrosis is a multisystem disease caused by mutations in the cystic fibrosis transmembrane conductance regulator gene. Mutations of this gene manifest as epithelial cell dysfunction in the airways, biliary tract, pancreas, gut, sweat glands, paranasal sinuses, and genitourinary tract. Viscous, inspissated bile causes ductal obstruction and hepatotoxicity from retained bile components, leading to fibrosis and ultimately cirrhosis, known as cystic fibrosis liver disease. LT is indicated in patients with decompensated liver cirrhosis. However, pulmonary disease is the main cause of morbidity and mortality in patients with cystic fibrosis [26]. One patient with cystic fibrosis in this series died of progressive respiratory failure 12 years after LDLT. Therefore, before undergoing LT, families need to be informed of the possibility of poor pulmonary outcomes.

Although heterozygous carrier donors are possible when performing LDLT for patients with OTCD, there is no consensus about the safety of LDLT from heterozygous carrier donors (**Table 3**) [10-13]. Rahayatri et al reported that the recipients have hyperammonemia after LDLT using grafts from asymptomatic heterozygous carrier donors [12]. Therefore, they concluded that the use of grafts from asymptomatic OTCD heterozygous donors in LDLT is acceptable with careful evaluation, and an OTCD heterozygous carrier donor should be avoided if there is another donor candidate. However, poor outcomes of DDLT from donors with unrecognized OTCD have been reported [27-29]. In our heterozygous carrier donor of OTCD, graft OTC activity of liver and GV/SLV was 104.4% and 54.0%, respectively [13]. Sufficient graft OTC activity of the liver and GV/SLV may be required. In addition, sufficient remnant volume for OTCD heterozygous carrier donors is required. We suggest that a donation from an OTCD heterozygous carrier donor should be avoided if there are another living donor candidate or deceased donor.

Information about disease incidence should be given to parents, but there are no specific recommendations. If a woman has an unplanned pregnancy without having received sufficient information, she may choose to undergo an abortion. In this study, of the younger siblings of 4 patients with neonatal hemochromatosis, 2 were born after the mother received antenatal maternal high-dose immunoglobulin treatment to prevent neonatal hemochromatosis [22]. One child whose mother did not receive immunoglobulin treatment who underwent LDLT from the puerperal mother developed neonatal hemochromatosis. Antenatal maternal high-dose intravenous immunoglobulin treatment has been reported to be effective for preventing neonatal hemochromatosis recurrence [30]. In younger siblings of patients with OTCD, carbamoyl phosphate synthetase 1 deficiency, MMA, and Niemann-Pick disease type C, 4 of the mothers had prenatal amniocentesis. Three siblings were healthy, and 1 sibling had OTCD and underwent DDLT. Therefore, information about antenatal maternal high-dose intravenous immunoglobulin treatment and prenatal amniocentesis should be carefully provided to the mother before pregnancy. In addition, genetic counseling will be required for the parents and recipients in the future. However, if siblings undergo LT for IMDs, it has been reported that later siblings should be listed and transplanted at a significantly younger age [31].

There is a potential for intellectual developmental disorders and neurological sequelae in patients with IMDs and hyperammonemia. However, the precise risk is unclear. In the present study, of 39 patients with IMDs (excluding 5 patients who have died), 15 patients (38%) had severe motor and intellectual disabilities in 4 patients, intellectual developmental disorders including epilepsy in 2, and attention-deficit hyperactivity disorder in 2. In addition, of 28 patients with IMDs, 13

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(46%) need special education. Kido has been reported that LT had limited effect for ameliorating neurodevelopmental outcome in patients with severe urea cycle diseases because hyperammonemia at the onset time already had a significant impact on the brain [32,33]. Therefore, novel neuroprotective measures should be developed to achieve better neurodevelopmental outcomes in these patients [32]. Moreover, Kido suggested that LT should be considered in patients with urea cycle diseases with maximum ammonia concentration <300 μmol/L at the time of disease onset to protect the brain [34]. In addition, further long-term social and educational follow-up for intellectual developmental disorder is needed in patients with IMDs after LT.

Conclusions

The long-term outcomes of LDLT in patients with IMDs are good. However, the long-term outcomes of LDLT in patients with IMDs who have metabolic defects expressed in other organs remain undefined and further follow-up is needed. In addition, long-term social and educational follow-up for intellectual developmental disorder is needed. This was a retrospective analysis from a single center. Continued evaluation of outcomes and accumulation of further experience are necessary.

Declaration of Figures Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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