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Liver Transplantation for Congenital Metabolic Disorders

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Abstract

Objective: The aim of the study is to identify the indications for and the outcomes of liver transplantation in congenital metabolic diseases.

Methods: Indications, survival, and complications of liver transplantation performed between July 2018 and September 2021 for congenital metabolic diseases were examined. Demographic information of patients, liver graft types, and donor information were included in the analysis.

Results: A total of 23 liver transplants were performed in 22 patients with a mean age of 7.3 ± 9.3 and a mean weight of 23.6 ± 21.7. The types and frequencies of liver grafts used for transplantation in this analysis include 18 left lateral sectors, 1 left lobe, 3 right lobes, and 1 deceased full-size liver. Two of the left lateral sectors were retrieved from deceased split liver grafts. Mortality was observed in 2 patients (9%), 1 in the early and the second in the late postoperative period. Excluding the 2 fatalities, 3 patients required reoperation due to issues with blood flow through the portal vein. Due to hepatic artery thrombosis, 1 patient required stent placement. Biliary tract complications developed in 5 (22%) patients with dilatation and stenting being performed by interventional radiology. The surviving patients (91%) had an uneventful postoperative course after discharge from the hospital.

Conclusion: Liver transplantation is increasingly used either as a definitive treatment method or to improve the course of the disease for metabolic diseases. With the high survival rates, reduction in the frequency of attacks, improved effects on growth, development, and nutrition, it is clear that liver transplantation is a valuable tool for use in congenital metabolic disorders. Examining appropriate patient selection and ideal timing for transplantation remain important issues for further examination.

Keywords: Congenital metabolic disorders, liver transplantation, pediatric liver transplantation

Introduction

Upon completion of the first successful liver transplantation (LT) by Starzl in 1963, he and his team subsequently completed the first successful pediatric liver transplantation.[1,2] The first successful pediatric LT with a living donor was publicized by Strong et al.[3] With the progression of medical knowledge and development of improved surgical techniques and post-operative care including immunosuppressive medication, LT has become the gold standard in the treatment of end-stage liver disease (ESLD) in adult and pediatric patients. Although childhood cholestatic diseases remain the most common cause in pediatric LT, there is a significant increase in the frequency of LT for congenital metabolic diseases (CMD).[4] The first LTs for metabolic diseases in childhood were completed in 1987 for liver failure caused by tyrosinemia followed by LT for a patient with a urea cycle disorder in 1989.[5,6] Today, CMD is the second most common clinical indication in pediatric LTs with or without ESLD. The goal of LT is to treat the pathological enzyme activity in CMD patients, reduce the severity of disease burden of halt progression of disease activity with a new liver containing sufficient enzyme activity.[7]

Materials and Methods

Patients with CMD who were referred to our transplantation clinic were included in the study.

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Liver Transplant Recipient Evaluation

All patients diagnosed with CMD who underwent liver transplantation were referred from pediatric or adult metabolic diseases or gastroenterology departments. All recipient patients were evaluated according to the routine LT preparation program applied in our clinic. This evaluation is composed of complete blood count, coagulation tests, comprehensive biochemistry analysis, tumor markers, viral serology, blood and urine cultures, as well as whole abdominal ultrasound (US), Doppler US, thorax and abdominal computed tomography (CT)/magnetic resonance (MR) examination with hepatic vascular reconstruction, lung function tests, and cardiac investigations. Where appropriate and based on the age of the patient, adult or pediatric gastroenterology, cardiology, pulmonology, or infectious disease consultations were made. Prior to progressing toward LT, all patients provided their informed consent.

Donor Evaluation

Donors had an age range of 18-65 and required blood group compatibility. Ethics committee approval was obtained from beyond fourth-degree relative donor candidates. Included in the analysis prior to donation were complete blood count, coagulation tests, coagulation-related genetic tests (Factor V Leiden and Prothrombin Gene mutation), comprehensive biochemistry analysis, tumor markers, viral serology, blood, and urine cultures. Liver parenchymal structure, vascular anatomy, biliary anatomy, and liver volumetry measurements were evaluated by CT angiography and MR cholangiography. Determination of donor liver lobe was made according to age and weight of the recipient. Contraindications for donation include liver fat content greater than 10% of the liver size, homozygous factor II, Factor V Leiden mutations, or systemic comorbidity.

Immunosuppression

Calcineurin inhibitors (tacrolimus or cyclosporine) and prednisolone-based protocol were used as post-transplant immunosuppressive therapy. Mycophenolate mofetil was added for increased immunosuppression as needed. Calcineurin inhibitor doses were adjusted based on the daily plasma level.

Follow-up

In the post-discharge period, the patients were followed up at least once a month in the first year and every 3-6 months after the second year. Treatment adjustments were made according to routine blood tests and plasma drug levels in outpatient follow-ups. Doppler US or CT angiography was performed as needed. Importantly, in regard to the metabolic disease, patients continued follow-up in the Pediatric Metabolism Diseases Department.

Results

A total of 178 patients underwent LT in our clinic between July 2018 and September 2021. Twenty-three LTs, including 1 re-transplantation, were performed on 22 patients with CMD. Two of these patients were adults (diagnosed with Wilson's disease) while the remaining LTs were pediatric patients. Demographic information, transplant indications, Model For End-Stage Liver Disease / Pediatric End-Stage Liver Disease (MELD/PELD), and child scores for cirrhotic patients and types of liver transplantations are summarized in Tables 1 and 2.

In 23 LTs, 16 of the biliary anastomosis were Roux-Y hepaticojejunostomy with the remainder using end-to-end bile anastomosis. All of the patients were extubated in the intensive care unit (ICU) postoperatively. The mean liver graft weight used in the patients was 375 ± 254 g, and the mean graft-to-recipient weight ratio was 2.1 ± 1.0%. The mean ICU stay of the patients was 4.5 ± 4.5 days, and the mean discharge time was on postoperative day 17.6 ± 6.8. The overall survival rate of the patients was 91% with a mean follow-up time of 1.5 ± 1.0 years.

Perioperative mortality was observed in 1 (4.5%) patient who underwent an LT for a urea cycle disorder (UCD). Acute portal vein thrombosis (PVT) occurred in this patient on post-transplant day 9, and left lateral sector split re-transplantation was performed from deceased liver donor in urgent conditions. Due to spontaneous intestinal perforations in post re-transplantation period, multiple laparotomies were performed and the patient died on post re-transplant day 13.

Late mortality was seen in 1 (4.5%) patient. The patient, who had a diagnosis of maple syrup urine disease (MSUD), underwent split cadaveric LT, and received combination rituximab and everolimus therapy for post-transplant lymphoproliferative disease associated with Epstein-Barr Virus infection. The patient further developed acute respiratory distress syndrome (ARDS) requiring extracorporeal membrane oxygenation treatment in the first year after transplantation, and the patient died shortly after this event. Infection was excluded as the etiology of ARDS, and the patient's lung failure was thought to be drug-related (everolimus).

Four patients developed vascular complications (18%). Included in these patients was the individual who underwent re-transplantation with acute PVT and died. In 1 patient, decreased portal vein flow and hepatic artery thrombosis were detected simultaneously in the intraoperative Doppler US controls. Portal vein and hepatic artery anastomosis revision was performed with a stent placed in the hepatic artery by interventional radiology because of persisting flow defects in the hepatic artery. Due to decreased portal vein flow, a different patient required a laparotomy for revision of the portal vein anastomosis. The last patient required stent placement in the portal vein by interventional radiology because of decreased portal vein flow. Excluding the deceased patient, these 3 patients were followed up with an average of 1.5 (2 years, 1.5 years, and 1 year) years, and their outpatient follow-up (including Doppler US controls) was uneventful.

Table 1. Patient Information of 22 Patients Who Underwent LT Due to CMD

Patients	22 (Male: 12/Female: 10)
Age (years)	7.3 ± 9.3
Weight (kg)	23.6 ± 21.7
BMI (kg/m^2)	18.5 ± 4.2
Type of transplantation	
Left lateral sector	16
Right lobe	3
Left lobe	1
Deceased full graft	1
Deceased left lateral sector	2
Diagnosis	
UCD	5
Wilson's disease	4
MSUD	4
MMA	2
Hypercholesterolemia	2
Tyrosinemia type 1	1
Glycogen storage type 4	1
Bile acid synthesis disorder	1
Crigler-Najjar	1
Cystic fibrosis	1

UCD, urea cycle disorder; MSUD, Maple syrup urine disease, MMA, methylmalonic academia.

Biliary complication was seen in 5 (22%) patients. Three patients had an early anastomotic leakage with a biliary stent being placed in 2 patients by percutaneous transhepatic cholangiography (PTC). Laparotomy was performed on the other patient due to high-flow leakage, and the end-to-end bile anastomosis was converted to a Roux-Y hepaticojejunostomy. Two other patients with late biliary stenosis were followed up with PTC and biliary stenting. All patients with biliary complications are continuing follow-up in the outpatient clinic without any further issues.

Intra-abdominal hemorrhage occurred in 1 patient requiring a laparotomy for control of bleeding and hemostasis.

Of the 23 LTs performed, 20 organs were retrieved from living donors with the remaining 3 obtained from deceased donors. Of the living liver donors, 15 were males and 5 were females; 17 donors were relatives up to the fourth degree. Three donors were distant relatives, requiring ethics committee approval for their donation. The mean age was 33.7 ± 8.2 years, and the

Table 2. Demographic, Disease, and Indication Information of Liver Transplant Patients

Patient	Age (years/months)	Sex (M/F)	Weight (kg)	BMI (kg/m²)	Diagnosis	Indications	PELD (<12 age)/MELD	Child-Turcotte-Pugh
1	5 years 1 month	F	19	17.6	Crigler Najjar type 1	Hyperbilirubinemia	13	7
2	3 years	M	14.1	17.8	Glycogen storage type 4	Uncontrolled hypoglycemia	4	6
3	4 years 10 month	F	17.8	15	Hypercholesterolemia	Hypercholesterolemia	Non-cirrhotic	-
4	4 years 11 month	F	12.9	16.3	Hypercholesterolemia	Hypercholesterolemia	Non-cirrhotic	-
5	12 year	M	28	16.1	Cystic fibrosis	Cirrhosis/portal hypertension	-4	5
6	7 years 8 month	F	17.7	15.2	MMA	Uncontrolled metabolism/kidney failure	Non-cirrhotic	-
7	1 year 2 month	M	6.5	15.4	MMA	Uncontrolled metabolism/growth retardation	Non-cirrhotic	-
8	2 years 6 month	M	14	16.9	MSUD	Uncontrolled metabolism/growth retardation	Non-cirrhotic	-
9	3 years 11 month	M	19.8	18.7	MSUD	Uncontrolled metabolism/growth retardation	Non-cirrhotic	-
10	8 years 8 month	M	18.5	23.9	MSUD	Uncontrolled metabolism/growth retardation	Non-cirrhotic	-
11	1 years 8 month	F	9.5	14.8	MSUD + Alport	Uncontrolled metabolism/growth retardation	Non-cirrhotic	-
12	6 months	M	5.8	18.5	Bile acid synthesis disorder	Hyperbilirubinemia/resistant itching	40	10
13	9 years 2 month	M	28	16.8	Tyrosinemia type 1 + HCC	HCC	-7	6
14	2 years 2 month	F	13.5	17.4	UCD	Hyperammonemia	Non-cirrhotic	-
15	1 year 1 month	F	6.7	18.6	UCD	Hyperammonemia	Non-cirrhotic	-
16	6 months	F	10.8	19.7	UCD	Hyperammonemia	Non-cirrhotic	-
17	7 months	M	8.6	16.1	UCD	Hyperammonemia	Non-cirrhotic	-
18	1 year 3 months	M	9.1	18.6	UCD	Hyperammonemia	Non-cirrhotic	-
19	13 years 2 months	M	57	18.4	Wilson's disease	Cirrhosis/portal hypertension	44	11
20	21 years 8 months	F	88	33.9	Wilson's disease	Cirrhosis/portal hypertension	38	10
21	41 years 2 months	F	66.9	24.6	Wilson's disease	Cirrhosis/portal hypertension	28	10
22	15 years 1 month	M	47.7	16.9	Wilson's disease	Cirrhosis/portal hypertension	27	8

HCC, hepatocellular carcinoma; MSUD, Maple syrup urine disease, MMA, methylmalonic academia; UCD, urea cycle disorder.

mean BMI was 25.2 ± 4.5. Left lateral sector resection was performed in 16 donors, right donor hepatectomy was performed in 3 donors, and left donor hepatectomy was performed in 1donor. The mean hospitalization time of the donors was 5.5 ± 1.2 days. A laparotomy was performed for a right lobe donor because of elevation in liver enzyme levels and suspected left hepatic artery stenosis although the peri-operative Doppler US identified good arterial flow. No major complications were observed in any other donations.

Discussion

The importance of LT in the treatment of CMD has increased significantly in recent years. A South American multicenter study showed that 14.9% of split liver transplants performed between 1995 and 2008 were for metabolic diseases with 25.6% of the cases having a diagnosis of UCD.[8] In addition to this study, the frequency of CMD was found to be 33.5% in pediatric liver transplants performed in the United States between 1997 and 2009.[9] These studies show that CMD is one of the most important indications for LT in pediatric patients.

Congenital metabolic diseases have 3 subgroups in terms of LT;

1- The enzyme defect is predominantly in the liver and led to ESLD because of this enzyme defect.

2- The enzyme defect is predominantly in the liver, which does not damage the liver itself, but can have catastrophic effects on other organs.

3- The enzyme deficiency in the liver is a part of the general enzyme deficiency in the whole body and can have widespread consequences.

Liver transplantation is a curative treatment option for diseases in the first and second groups, and after a successful LT, patients live a normal life. In the third group of diseases, LT is cannot be curative as it is systemic. In this patient subgroup, by increasing enzyme activity, the goal is to produce a milder progression of the disease, decreasing attack incidence, better growth development, and reducing other organ involvement. This can create a better quality of life for the patient.[10] Importantly, for the patients in this subgroup, coordination with the pediatrics metabolism department is crucial to prevent further attacks and metabolic decompensation after LT, as the disease progresses.

Our patients with diseases in the first and second group (UCD, Wilson's disease, hypercholesterolemia, tyrosinemia, glycogen storage disease, bile acid synthesis disorder, and Crigler-Najjar disease) returned to normal life with proper nutrition and no added dietary requirements, after liver transplantation.

Since the systemic diseases of the third group (MSUD and MMA) patients continued after the transplantation, nutritional protocols and drug treatments were adjusted with the metabolic diseases department. These patients were followed up with blood gas, serum ammonia, and amino acid levels to determine metabolic decompensation, notably in the early post-transplant period. Total parenteral nutrition containing 2 g/kg/day protein was started from the first day of the preoperative period and it was gradually decreased with increasing oral intake. As a nutritional protocol, the transition to age-appropriate food was started with 0.5 g/kg/day protein intake and gradually increased to 2 g/kg/day, and they were discharged with protein-restricted normal nutrition.[11,12]

In the postoperative period, the patient with decompensated liver disease due to cystic fibrosis (with bronchiectasis in the lungs) was followed closely by the pediatric pulmonology department. Salt restriction continued in the post-transplant period for this patient. Weekly evaluation of sputum cultures to identify pneumonia and sensitivities of the bacteria for determination of antibiotic treatment were conducted. In addition, the removal of secretions with respiratory physiotherapy was important in the postoperative follow-up.

Although Wilson's disease is a congenital metabolic disease, clinical findings can be seen at various ages. In addition to acute liver failure, chronic liver disease and central nervous system involvement are the most common clinical manifestations.[13] Four of the patients in our series had a diagnosis of Wilson's disease. Two of them were in the pediatric age group while the remainder were adults.

Hepatocellular carcinoma (HCC) is another important factor in CMDs. Although it is frequently seen in patients with tyrosinemia type-1, glycogen storage diseases, and alpha-1 antitrypsin deficiency, it can be seen in various metabolic diseases affecting the liver through inflammatory processes.[14] Notably, in tyrosinemia and glycogen storage diseases, HCC can develop before liver failure symptoms. This knowledge necessitates the need for monitoring with alpha-fetoprotein and radiological imaging for tumor monitoring.[14,15] One of the patients, who underwent LT due to HCC with tyrosinemia type-1 origin, is 9 years old (Figure 1). This patient was transplanted without signs of liver failure, and outpatient follow-up was uneventful after 3 years post-transplantation.

There is a significant role for LT in the treatment of metabolic diseases. In addition, LT brings its own morbidity and mortality, the necessity of life-long immunosuppressive medication, susceptibility to infections, and toxic effects of these aforementioned medications. Collaboration with the pediatric and metabolic diseases department provides for adequate patient selection and determination of appropriate indications for LT.

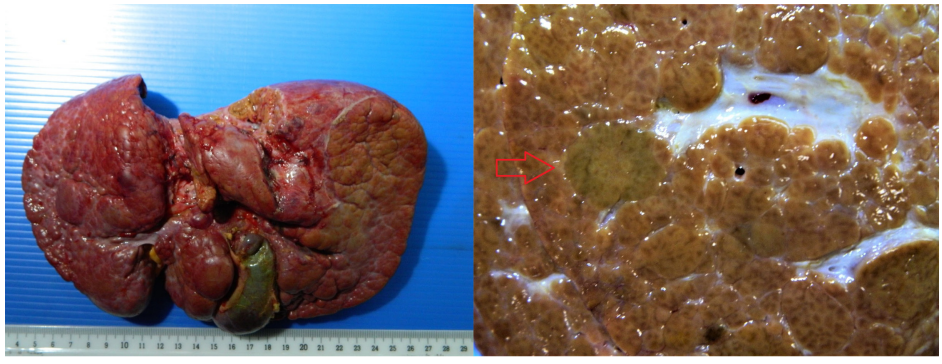

Figure 1. Macroscopic findings of a patient with Tyrosinemia Type 1 without liver failure who underwent liver transplantation for HCC.

Conclusion

Liver transplantation is a good treatment option for patients with CMD with survival rates of over 90%. In particular, LT with living donors offers a customizable operative program and donor selection. Most importantly, after attaining metabolic stabilization, the patient can undergo transplantation in the most ideal conditions.

Ethics Committee Approval: The study was conducted conform to the Declaration of Helsinki criteria as well as Declaration of Istanbul criteria. The study was performed as a retrospective study with anonymized data analyses for which IRB approval was waived.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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