

Pediatric Liver Transplantation as Enzyme Replacement Therapy for Rare Metabolic Diseases with No Structural Liver Damage

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This study has not been presented previously in a congress or symposium.

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<https://doi.org/10.32552/2021.ActaMedica.672>

Received: 16 August 2021, Accepted: 23 September 2021,
Published online: 28 September 2021

ABSTRACT

Objective: Very rare monogenic metabolic diseases without structural liver damage can be cured by liver transplantation. This process is a surgical enzyme replacement therapy, and defective enzymes may or may not be confined to the liver. The aims of this single center study of children with metabolic diseases showing structurally normal liver parenchyma were to analyze the indications and post-operative outcomes of liver transplantation, identification of developmental and metabolic benefits of the procedure with recognition of peri-operative difficulties to improve the success rate.

Materials and Methods: Patients under the age of 19-year-old who underwent liver transplantation for metabolic disorders with no structural liver injury between January 2015 and June 2021 analyzed retrospectively. Patient and graft survivals, indications for transplantation, presence of extra-hepatic enzyme deficiency causing other organ damage, inclusion of simultaneous or sequential kidney transplantation, immunosuppressive protocols, post-transplant complications, and metabolic outcomes were identified.

Results: Eight children with primary hyperoxaluria type 1 (n = 4), Maple syrup urine disease (n = 1), Crigler-Najjar syndrome type 1 (n=1), familial hypercholesterolemia (n=1) and propionic acidemia (n = 1) received left lobe (n=6) and left lateral segment (2) allografts from living donors. The median age of 4 girls and 4 boys at time of transplantation was 6.8 years (range 2.2-12.7 years). The median follow-up time was 3.3 years (range 1.5-5.7 years). The most common post-transplant complications were biliary system complications and infections and, two patients died because of sepsis. Six patients are alive with normal functioning allografts and metabolically stable on unrestricted diet.

Conclusion: Liver transplantation is a lifesaving treatment and improves patient's and parent's life quality for metabolic disorders with no parenchymal injury despite strict dietary restrictions and medical therapies. Especially, living donor liver transplantation is very important for populations with very low organ donation rates.

Keywords: Living donor liver transplantation, children, metabolic disease

INTRODUCTION

Very rare monogenic metabolic diseases without structural liver damage can be cured by liver transplantation (LT). This process is a surgical enzyme replacement therapy, and the defective enzymes may or may not be confined to the liver (Table-1). Transplantation decision is simple for metabolic disorders with liver injury leading liver failure, but systemic consequences of deficient enzymes are the main reasons for LT when there is no liver distortion in histological evaluation. Transplantation might be a lifesaving or an organ saving procedure and/or an option for better quality of life due to severe systemic manifestations in this particular group of patients [1-9].

The aims of this single center study of children with metabolic diseases presenting structurally normal liver parenchyma were to analyze the indications, appropriate timing and post-operative outcomes of liver transplantation, identification of developmental and metabolic benefits of the procedure along with recognition of peri-operative difficulties to improve the success rate.

MATERIALS and METHODS

Between January 2015 and June 2021, patients under the age of 19-year-old who underwent liver transplantation at Acibadem University Hospital with diagnosis of metabolic disorders without structural liver damage were analyzed retrospectively. Operative techniques, patient and graft survivals, post-transplant surgical and medical complications, immunosuppressive protocols, and metabolic status of patients were identified. Donor

and recipient characteristics were documented at time of transplantation and descriptive statistics were defined as median with minimum and maximum values. Patient and graft survivals were given according to primary diagnoses of the patients.

This study was approved by institutional review board with 2021/11-21 protocol number.

RESULTS

Between January 2015 and June 2021, eight children with five different hereditary metabolic disorders with no liver injury received liver allografts via living donor liver transplantation (LDLT). These included primary hyperoxaluria type 1 (PHO1, n = 4), Maple syrup urine disease (MSUD, n = 1), Crigler-Najjar syndrome type 1 (CN1, n=1), familial hypercholesterolemia (FHC, n=1) and propionic acidemia (PA, n = 1). Six patients received left lobes (LL) and 2 were transplanted with left lateral segments (LLS) from living related donors. The median age of 4 boys and 4 girls at time of transplantation was 6.8 years (range 2.2-12.7 years). The body weight distribution of the patients was 18.7 kg median weight with range of 9.4-36 kg. The median follow-up time was 3.3 years (range 1.5-5.7 years) after LDLT. Two patients with PHO1 died because of pneumonia related sepsis and urinary sepsis at 0.15 and 3.9 years respectively after their transplantations. Other 6 patients are alive with normal liver function on mono or dual immunosuppressive therapies. All patients are metabolically stable on unrestricted diet. There

Table 1. Classification of liver-based metabolic disorders with normal liver parenchyma [1-9], (*Argininosuccinic aciduria).

Metabolic disease with no structural liver injury	
Deficient enzyme confined to the liver	Extra-hepatic involvement of deficient enzyme
Crigler-Najjar syndrome type 1	Maple syrup urine disease
Primary hyperoxaluria type 1	Methyl malonic acidemia
Urea cycle disorders (except ASA*)	Propionic acidemia
Familial hypercholesterolemia	
Hemophilia	
Factor VII deficiency	
Protein C and S deficiencies	
Factor H deficiency	
Amyloidosis type 1	

was no portal vein or hepatic artery thrombosis, and no re-transplantation was performed. Bile leak in 3 patients was resolved after drainage (n=1), and revision of biliary reconstruction (n=2). Biliary stricture following bile leak was resolved by percutaneous transhepatic cholangiography (PTC) with balloon dilatation in one patient. Patient and donor characteristics, technique details and postoperative period are summarized in Table-2 and 3.

DISCUSSION

Monogenic metabolic disorders are the second most common disease group for pediatric liver transplantation after biliary atresia. LT rate for metabolic disorders increased from 10% to 16% in last decade and still comprises 12.6% of the pediatric waitlist. Five-year patient and graft survival rates were given as 88-95% in OPTN/SRTR data for metabolic diseases with deceased donor liver transplantation and more than 70% varying with the primary diagnosis according to LDLT reports [1-3, 10-12]. Inherited metabolic diseases with normal liver parenchyma may benefit from LT if they cause multisystemic consequences due to deficient enzymes. Indications and outcomes for LT differ according to extra-hepatic manifestations.

Primary hyperoxaluria type 1 is an autosomal recessive metabolic disorder caused by alanine glyoxylate aminotransferase (AGT) enzyme

deficiency. AGT is a liver peroxisomal enzyme and deficiency causes increased oxalate production and urinary excretion. Oxalate accumulates in bone, skin, arteries, heart, peripheral nerves and retina causing systemic oxalosis. Calcium oxalate crystals are deposited in kidneys and impairs renal function. Pyridoxine, hyperhydration, citrate, neutral phosphate and diuretics might be used to delay the progression of renal disease. Unfortunately, peritoneal and hemodialysis are not effective in removal of oxalate but may slow down systemic oxalosis prior to the transplantation. PHO1 can be cured by LT after total native hepatectomy. Isolated kidney transplantation is not recommended since disease recurs because of enzyme deficient native liver. Partial native hepatectomy and auxiliary LT is contraindicated in PHO1 due to enzyme deficient residual native liver. Blood and urinary oxalate levels are normalized after LT if there is no systemic oxalosis with normal renal function. Preemptive isolated LT may be considered when GFR is between 40-60 ml/min/1.73m², but combined liver and kidney transplantation is strongly recommended if GFR falls below 40 ml/min/1.73m². However, the mobilization and urinary excretion of the oxalate load lasts months to years in case of systemic oxalosis. Simultaneous liver and kidney transplantation may cause impairment of renal graft with existing systemic oxalosis load despite immunological benefits of the procedure. Sequential liver and kidney transplantation might be considered to reduce the systemic oxalate

Table 2. Patient characteristics (*age at transplantation, years, †male, ‡female, § age at diagnosis, years).

Case number	Primary diagnosis	AAT*	Gender	AAD _§	Comorbidities	Pre-transplant therapies
1	PHO1	6.3	M†	4	Nephrocalcinosis, Severe systemic oxalosis, Failure to thrive	Pyridoxine, hemodialysis
2	PHO1	6.7	M	4	Urolithiasis, Nephrocalcinosis, Severe systemic oxalosis	Pyridoxine, hemodialysis
3	PHO1	10.3	M	2	Urolithiasis	Pyridoxine, hemodialysis
4	PHO1	10.4	F‡	5	Urolithiasis, Nephrocalcinosis, Severe systemic oxalosis	Pyridoxine, hemodialysis
5	MSUD	6.9	F	At birth	Poor neurocognitive function	Protein restricted diet (noncompliant)
6	CN1	12.7	F	8	Poor school performance	No therapy
7	FHC	4.4	F	4	Aortic valve calcification and mild insufficiency	Statins, omega-3, coenzyme-Q
8	PA	2.2	M	At birth	-	Protein restricted diet

Table 3. Patient, donor and allograft characteristics and surgical, medical and metabolic outcomes (*grams, †body weight at transplantation, kilograms, ‡post-operative day, ¶ post-operative month, § post-operative year, || living donor kidney transplantation, **cyclosporin A, ††laparotomy, †††ureteroneocystostomy).

Case number	Allograft type and weight (gr*)	BWAT (kg†)	Donor	Biliary anastomosis	Surgical complications	Medical complications	Follow up (years)	Outcomes
1	LL/310	8	Mother	HJ	Bile leak resolved by drainage at POM1 ¶	Sepsis, prolonged intubation-tracheostomy	0.15	Exitus because of pneumonia at POM2 before LDKT
2	LL/330 LDRT (simultaneous)	14	Mother	HJ	L/T†† for intraabdominal bleeding at POD0‡, UNC‡‡ for ureteral stricture at POM4	-	3.60	Alive with normal liver and kidney function on tacrolimus
3	LL/420 LDRT (simultaneous)	30	Father	HJ	Seroma around renal graft resolved by drainage at POM2	Seizures with tacrolimus	3.79	Alive with normal liver and kidney function on tacrolimus
4	LL/285 LDRT (sequential, 4 months apart)	20	Mother	Duct-to-duct	Ureteral stricture at POD15 resolved by nephrostomy catheterization and dilatation, resistant ascites resolved by splenic artery embolization	Renal graft failure due to preexisting systemic oxalosis at POY2 and hemodialysis requirement	3.96	Exitus because of urinary sepsis at POY4
5	LL/-	21	Mother	Duct-to-duct	Bile leak resolved by biliary reconstruction at POD2	-	5.73	Alive with normal liver function on unrestricted diet and tacrolimus-cycA**
6	LL/450	28	Mother	HJ	Bile leak resolved by biliary reconstruction at POD25, L/T for adhesive obstruction at POM2	-	3.01	Alive with normal liver function on tacrolimus
7	LLS/360	17.5	Cousin	Duct-to-duct	-	-	2.58	Alive with normal liver function on tacrolimus, normal cholesterol levels with no medication
8	LLS/270	9.4	Father	HJ	L/T for jejunal perforation at POD7, biliary stricture resolved by PTC and dilatation	-	1.53	Alive with normal liver function on unrestricted diet and tacrolimus

load by hemodialysis after LT, but dialysis is not an effective way of oxalate removal by any means [1, 13-19]. Native nephrectomy may also help decreasing amount of mobilized oxalate and urinary stone complications in case of combined transplantation. LDLT and LDKT especially from same donor either simultaneous or sequential are favorable in terms of immunological point of view but needs to be assessed very carefully about risks for the donor. Previously we reported our experience with 4 pediatric and one adult PHO1 patients [20]. We lost two of four pediatric patients at post-transplant 2nd month and 4th year due to severe pneumonia and urinary sepsis. Patient with urinary sepsis had renal allograft failure at second year due to preexisting systemic oxalosis mobilization, excretion and accumulation at renal graft.

Maple syrup urine disease (MSUD) is an autosomal recessive inherited disorder with defect in the branched-chain alpha ketoacid dehydrogenase (BCKDH) complex. Valine, leucine, and isoleucine amino acids cannot be fully metabolized, and toxic metabolites cause metabolic decompensation despite aggressive therapy with dietary restriction of affected amino acids and dietary supplements. Neurocognitive function continues to decline any time when metabolic crises and cerebral edema occur during episodes of common infections and injuries. Liver transplantation is demonstrated to be effective in neurodevelopmental status of classical/severe MSUD besides improving children's and families' quality of life due to severe protein restriction and frequent hospitalizations. LT is crucial especially for patients with poor access to health centers with metabolic disease experts. LT cures the disease but cannot reverse existing spasticity, dystonia, or mental retardation. It is important to inform families of patients with poor metabolic control about LT option before irreversible neurological complications occur. Mazariegos et al reported 100% patient and graft survival in their 35-patient series at 4.5 ± 2.2 years of follow-up period. MSUD patients with normal liver function tests are also good candidates for domino liver transplantation [2,3,8,21-23]. We performed LDLT for one patient with already declined neurocognitive function since patient was not compliant with her diet and experienced multiple episodes of metabolic crises. She underwent LT at age of 6.9 years. She is metabolically stable on

unrestricted diet and no further neurocognitive deterioration was reported during her post-transplant follow up.

Propionic academia is an autosomal recessive inherited metabolic disease with defective propionyl-CoA carboxylase enzyme. Although there is partial correction of metabolic defect, liver transplantation is indicated in case of frequent metabolic crises despite optimum medical therapy to improve the quality of life and limit the neurocognitive impairment and/or cardiomyopathy. Barshes et al reported 72% patient survival in their review after LT on unrestricted diet. Generally, organic acidemia patients are allowed to have approximately 0.8 grams protein/kg body weight protein-limited diet or specially designed enteral formulas [1,24-26]. We transplanted one patient with PA who had very early diagnosis and started strict diet with medical therapy. Unfortunately, patient experienced multiple hyperammonemia episodes and hospitalizations at times of simple infections and injuries. Patient received LDLT at age of 2.2 and had no metabolic crises since then on unrestricted diet.

Crigler-Najjar syndrome type 1 is a rare autosomal recessive inherited metabolic disorder with severe indirect hyperbilirubinemia. Total deficiency of uridyl-diphosphate glucuronosyl transferase enzyme (UGT1A1) activity causes accumulation of unconjugated bilirubin leading severe encephalopathy. Patients require phototherapy to decrease bilirubin levels and prevent irreversible kernicterus. Despite prolonged phototherapy (12 to 20 hours/day), the children remain jaundiced, and neurologic damage may occur at any time and more than 20% of young adults develop permanent neurological lesions under extensive phototherapy. Thirty percent hepatic UGT1A1 activity is required to preserve normal bilirubin homeostasis in total body and LT is recommended as a cure within the first year of life before the onset of neurological sequela besides improving patients' and families' quality of life. Strauss et al reported 100% patient and graft survival in their 16 CN1 patient series with normal bilirubin levels [1,27]. We performed LDLT for one CN1 patient who was diagnosed very late and neurologically affected with poor school performance. Patient was treated as Gilbert syndrome until 8 years old and after that she was on no therapy. Her indirect bilirubin levels were

around 17-18 mg/dL at time of transplantation and normalized in 12 days at post-operative follow up. Her school success has been improved drastically since LT with normal bilirubin levels.

Familial hypercholesterolemia is an autosomal dominant inherited disorder characterized by isolated elevation of plasma low-density lipoprotein (LDL) cholesterol. LDL receptor defects or anomalies of Apolipoprotein B cause high plasma LDL cholesterol levels and it is associated with high risk of very early cardiovascular problems. LT is indicated before advanced cardiovascular disease to minimize the operative risks and to avoid combined heart and liver transplantation. Near normal levels of LDL receptors and cholesterol can be achieved since normal liver contains 50-75% of LDL receptors but statin use might be required after the transplantation to maintain completely normal blood cholesterol levels. LDLT is a good option in regions with limited deceased donation but it might be hard to find a normolipidemic living related donor and parents are deemed as unsuitable candidates since they might be undiagnosed FHC heterozygotes in homozygous FHC cases. There are controversial statements in the literature but many successful LTs with normolipidemic heterozygote parental donors were reported with or without need of statin use in their post-transplantation follow up. Unfortunately, side effects of immunosuppressant therapies can also give rise to renal damage,

heart failure, and bone marrow suppression and especially cyclosporine may cause hyperlipidemia but according to literature 10-year survival rate exceeds 70% [1,28-33]. We performed LDLT for one homozygous FHC patient from her cousin. Patient's parents were heterozygotes for LDLR gene mutation with slightly high cholesterol levels. Patient was diagnosed at age of 4 years and was already affected with very high LDL cholesterol levels. Her cardiac work up showed aortic calcification and mild aortic insufficiency with intimal thickening in bilateral common carotid arteries. Patient's lipid profile was normalized and stayed normal with no statin use after LT.

As a conclusion, liver transplantation is a lifesaving treatment and improves patients' and parents' quality of life for children with metabolic disorders with no parenchymal injury despite dietary restrictions and several medical treatment modalities. Timing of the liver transplantation is crucial not to allow for neurocognitive and other organ impairment. Especially, LDLT is a good option for populations with very low organ donation rates enabling appropriate timing of the operation with extra immunological benefits.

CONFLICT of INTEREST

No conflict of interest was declared by the authors.

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