Turkish Journal of Pediatric Disease
Türkiye Çocuk Hastalıkları Dergisi

Pediatric Liver Transplantation For Hereditary Metabolic Disorders With Structural Liver Damage

Karaciğer Parankim Hasarı ile Seyreden Kalıtımsal Metabolik Hastalıklarda Pediatrik Karaciğer Nakli

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ABSTRACT

Objective: Variety of inherited metabolic diseases with or without liver parenchymal injury can be cured by liver transplantation and this process is actually a surgical enzyme replacement therapy for the defective protein. The aim of this single center study was to analyze the liver transplantation indications, post-transplantation outcomes with benefits of the procedure, and also identification of the problems encountered during the process to improve the success rate in pediatric metabolic diseases with liver parenchymal damage.

Material and Methods: We retrospectively reviewed the records of children who underwent liver transplantation because of metabolic disorders with liver parenchymal damage from January 2015 to June 2021. Data collected included patient and donor demographics, operative techniques, patient and graft survivals, post-transplant surgical and medical complications, and immunosuppressive protocols.

Results: Fourteen children with progressive familial intrahepatic cholestasis (n = 8), Alagille syndrome (n = 3), tyrosinemia type-I (n=1), familial neonatal hepatitis (FNH, n=1) and glycogen storage disease type-I (GSD-I, n = 1) received left lateral segment (n=10), right lobe (n=2), reduced size left lateral segment (n=1), and mono-segment (n=1) allografts from living donors. The median age of 5 boys and 9 girls at time of transplantation was 42.3 months (range 6.9-215.5 months). One patient with FNH was lost to follow and excluded from the study. The median follow-up time was 12.7 months (range 0.4-53.4 months) and we lost four patients because of sepsis. Most common post-transplant complications were acute cellular rejection and infections.

Conclusion: Liver transplantation is a lifesaving treatment for patients with metabolic disorders comprising liver failure, malignancies, and associated complications despite several medical and surgical treatment modalities.

Key Words: Child, Liver transplantation, Metabolic diseases

ÖZ

Amaç: Çeşitli enzim eksikliklerileyle seyreden doğumsal metabolik hastalıklar, karaciğer parankim hasarının varlığından bağımsız olarak karaciğer nakli ile tedavi edilebilirler ve bu endikasyonlarda karaciğer nakli, cerrahi bir enzim replasman tedavisidir. Tek merkezli bu çalışmanın amacı, karaciğer parankim hasarı ile seyreden metabolik hastalıklı çocuklarda karaciğer nakil endikasyonlarını ve nakil sonrası sonuçları incelemek; tedavinin yararlarını ve başarı oranlarını artırmak için bu süreçte yaşanılan zorlukları ortaya koymaktır.

Gereç ve Yöntemler: Ocak 2015 ve Haziran 2021 tarihleri arasında karaciğer parankim hasarı ile seyreden doğumsal metabolik hastalık tanısıyla karaciğer nakli yapılan 19 yaş altı hastalar, retrospektif olarak incelendi. Hasta ve greft sağ kalım oranları, transplantasyon endikasyonları, immünsupresif protokoller, nakil sonrası erken ve geç dönemdeki cerrahi ve medikal komplikasyonlar incelendi.

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. For the study, Acıbadem University 24.06.2021 protocol date and 2021/11-19 approval document.

Contribution of the Authors / Yazarların katkısı*: *CELIK N: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***EMIROGLU R:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Celik N and Emiroglu R. Pediatric Liver Transplantation For Hereditary Metabolic Disorders With Structural Liver Damage. Turkish J Pediatr Dis 2021;15:408-414.

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Received / Geliş tarihi : 09.08.2021
Accepted / Kabul tarihi : 07.09.2021
Online published : 10.09.2021
Elektronik yayın tarihi
DOI: 10.12956/tchd.979822

Bulgular: Progresif familial intrahepatik kolestaz (n=8), Alagille sendromu (n=3), tirozinemi tip-1 (n=1), ailevi neonatal hepatit (n=1) ve glikojen depo hastaligi tip-1 (n=1) tanılarıyla, 14 hastaya sol lateral segment (n=10), sağ lob (n=2), küçültülmüş sol lateral segment (n=1) ve monosegment (n=1) greftlerle canlı vericili karaciğer nakli gerçekleştirildi. Ortanca yaşı 42.3 ay (6.9-215.5 ay) olan 5 erkek ve 9 kız hastadan, familial neonatal hepatit tanılı hasta takipten çıktığı için verilerine ulaşılamadı. Ortanca takip süresi 12.7 ay (0.4-53.4 ay) olarak hesaplandı. Sepsis nedeniyle 4 hasta kaybedildi ve akut selüler rejeksiyon ve enfeksiyonlar en sık postoperatif komplikasyonlar olarak belirlendi.

Sonuç: Karaciğer nakli, genetik geçişli metabolik hastalıklarda mevcut medikal ve cerrahi tedavi olanaklarına rağmen karaciğer yetmezliği, malignensi gelişimi ve ilişkili komplikasyonların oluşması durumunda hayat kurtarıcı bir prosedürdür.

Anahtar Sözcükler: Çocuk, Karaciğer nakli, Metabolik hastalık

INTRODUCTION

Variety of inborn errors of liver metabolism with or without liver injury can be cured by liver transplantation (LT). Distortion in the liver parenchyma may occur in forms of steatosis, fibrosis or cirrhosis, adenomas or hepatocellular carcinoma (HCC) caused by deficient enzyme related protein malformations. These liver-based metabolic disorders represent about 10-15% of the primary indications for pediatric LTs being the second most reason after biliary atresia. LT is actually a surgical enzyme replacement therapy for this group of patients and deficient enzymes may or may not confined to the liver (1-8, Table I).

Despite the early diagnosis and advances in therapies for metabolic disorders, LT is still a lifesaving procedure. With this single center study, we aimed to analyze the liver transplantation indications, appropriate timing, post-transplantation outcomes and benefits, and identification of the problems encountered to improve the success rate in pediatric metabolic diseases with liver parenchymal damage.

MATERIAL and METHODS

Patients under the age of 19-year-old who underwent liver transplantation at Acibadem University Hospital because of metabolic diseases with structural liver damage were analyzed retrospectively between January 2015 and June 2021. Operative techniques, patient and graft survivals, post-transplant early and late surgical and medical complications, immunosuppressive protocols were identified. Donor and recipient characteristics were recorded at time of transplantation and descriptive statistics were described as median with minimum and maximum values. Kaplan-Meier test was used for survival analysis.

This study was approved by institutional review board with 2021/11-19 protocol number.

RESULTS

Between January 2015 and June 2021, fourteen children with five different hereditary metabolic disorders causing structural liver damage underwent liver transplantation. These included progressive familial intrahepatic cholestasis (PFIC, n=8), Alagille syndrome (AS, n=3), tyrosinemia type-I (TT-I, n=1), familial neonatal hepatitis with delta 4-3 oxosteroid 5-beta reductase deficiency (FNH, n=1) and glycogen storage disease type-I (GSD-I, n=1). Living donor liver transplant (LDLT) was the operative choice for all cases comprising left lateral segment (LLS, n=10), right lobe (RL, n=2), reduced size LLS (n=1), mono-segment (MS, n=1) allografts. The median age of 5 boys and

Table I: Classification of liver-based metabolic disorders with structural liver damage (2-8).

Metabolic disease with structural liver damage	
Deficient enzyme confined to the liver	**Extra-hepatic involvement of deficient enzyme**
Alpha-1 anti-trypsin deficiency	Wilson disease
Tyrosinemia type 1	Alagille syndrome
Indian childhood cirrhosis	Galactosemia
Idiopathic copper toxicosis	Erythropoietic porphyria
Hepatic porphyrias	Glycogen storage disease types Ib, III and IV
Neonatal haemochromatosis	Lysosomal storage diseases
Glycogen storage disease type Ia and 4a (GBE1 gene)	Gaucher disease
PFIC types 2 and 3	Niemann-Pick disease
Primary bile acid synthesis disorders	Cholesterol ester storage disease
Hereditary fructose intolerance	Cystic fibrosis
	Mitochondrial respiratory chain disorders
	PFIC type 1
	Non-alcoholic steatohepatitis
	Cerebrotendinous xanthomatosis
	Citrin deficiency

Table II: Patient characteristics.

Case	Primary diagnosis	AAT (mo)	Gender	Age at diagnosis (mo)	Comorbidities	Pre-transplant therapies
1	PFIC 2	43.5	M	11	Left renal hypoplasia, proteinuria, hypertension, pancytopenia	UDCA Patient was in PICU and intubated at time of transplant
2	PFIC (type N/A)	36.8	F	1	Mild PS	UDCA
3	PFIC 3	76.6	F	6	Chronic lung disease, renal failure	Patient was in PICU and intubated
4	PFIC (type N/A)	6.9	F	1	-	UDCA
5	PFIC 3	29.3	F	6	-	UDCA
6	GSD 1	40.9	F	1	-	Frequent feeds, diet
7	Alagille syndrome	64	M	1	Dysmorphic face	UDCA
8	PFIC 1	215.5	M	24	-	UDCA
9	Alagille syndrome	34.3	F	2	-	UDCA
10	PFIC (type N/A)	8.1	F	1	-	UDCA
11	Alagille Syndrome	14.2	F	1	Minimal pericardial effusion	UDCA, portoenterostomy with misdiagnosis as biliary atresia
12	PFIC 3	198.6	M	5	-	UDCA
13	TT-1	56	F	11	-	UDCA, NTBC, diet

MO: *Months,* ***UDCA:*** *Ursodeoxycholic acid,* ***PICU:*** *Pediatric intensive care unit,* ***N/A:*** *Not available,* ***F:*** *Female,* ***M:*** *Male,* ***PS:*** *Pulmonary stenosis,* ***NTBC:*** *2-(2-nitro-trifluoromethyibenzoyl)-1,3-cyclohexenedione*

9 girls at time of transplantation was 42.3 months (range 6.9-215.5 months). The body weight distribution of the patients was 13 kg median weight with range of 6.7-72 kg. Parents were the donors including 9 mothers and 4 fathers besides one unrelated donor. One patient with familial neonatal hepatitis with delta 4-3 oxosteroid 5-beta reductase deficiency was lost to follow up and excluded from the study for further analysis. Four patients died at median follow-up time of 12.7 months (range 0.4-53.4 months) after LDLT. Three patients with PFIC died because of sepsis 0.4, 0.9 and 12.7 months after transplantation. One patient with AS died due to an unknown reason after her transfer to home country. Other 10 patients are alive with normal liver function on mono or dual immunosuppressive therapy. There was no portal vein or hepatic artery thrombosis, and no re-transplantation was performed. Biliary leak occurred in one patient and was resolved with drainage. Kaplan-Meier patient and graft survival rate at one year was 65%. Patient and donor characteristics, technique details and postoperative period are summarized in Table II -III.

DISCUSSION

Metabolic diseases are the second most common reason for liver transplantation in pediatric age group after biliary atresia. Metabolic disease livers might be structurally normal or damaged causing liver and/or other organ failure because of deficient enzymes. Therefore, liver transplantation is a lifesaving procedure for patients with metabolic diseases comprising liver parenchymal damage since transplanted healthy liver with normal enzyme levels improves both genetic and functional failing. Commonly these disorders including PFIC and Alagille syndrome are named under cholestatic liver diseases but enzyme deficiencies resulting protein defects are the actual reason for liver distortion.

The patient and graft survival rates for PFIC patients were given as 85.2% and 76.6% respectively according to the literature up to 19 years post-transplant follow up period (8). All to the better, Englert et al successfully reported 100% patient and graft survival in their series with 23 patients who underwent biliary diversion prior to the transplantation (9). PFIC patients might benefit from other medical and surgical treatment modalities to some extend such as urso-deoxycholic acid (UDCA), cholestyramine and rifampicin, and biliary diversion. UDCA increases bile acid excretion from hepatocytes and inhibits their intestinal reabsorption limiting bile acid return to liver. Cholestyramine and rifampicin aid fecal and urinary bile salt excretion providing symptomatic relief for pruritis. Biliary diversion procedures might reduce severe pruritis and slow down the progression of fibrosis when performed early by decreasing the enterohepatic circulation of bile and its toxic effects. However, transplant becomes the only treatment when cirrhosis occurred and there will be no real benefit from alternative managements (10-16). In our series 9 PFIC patients underwent LDLT with decompensated cirrhosis, refractory ascites, severe malnutrition and history of multiple cholangitis episodes. Pruritis was very prominent but end stage liver disease was the main indication for LDLT. Very poor pre-transplant condition with chronic lung disease, decompensation with multiple arterial cloths early after

Table III: Patient, donor and allograft characteristics and outcomes.

Case	Allograft type and weight (g)	BWAT (kg[s])	Donor	Biliary anastomosis	Surgical complications	Medical complications	Follow up (mo)	Outcomes
1	LLS/340	11	Mother	Duct-to-duct	Biliary leak and pleural effusion at POM1	ACR at POD7	53.4	Alive with normal liver function on tacrolimus
2	LLS/320	14	Mother	Hepaticojejunostomy	Wound infection at POW1	HTN, febrile neutropenia with UTI at POM3	50.4	Alive with normal liver function on tacrolimus
3	LLS/330	18	Unrelated	Duct-to-duct	-	Sepsis	0.9	Exitus at 0.9 mo with sepsis
4	LLS/270	6.8	Father	Hepaticojejunostomy	Duodenum perforation at POD5, diaphragmatic hernia with obstructed colon at POM5		36.2	Alive with normal liver function on tacrolimus
5	LLS/210	7.8	Mother	Hepaticojejunostomy	-	-	29.4	Alive with normal liver function on tacrolimus
6	LLS	12	Mother	Hepaticojejunostomy	-	Sepsis at POW8, influenza-A at POM6	24.4	Alive with normal liver function on normal diet and cycA
7	LLS/305	10	Mother	Hepaticojejunostomy	GIS bleeding from jejunojejunostomy	ACR at POW7	24.3	Alive with normal liver function on tacrolimus and MMF
8	RL/740	43	Mother	Duct-to-duct	Incarcerated umbilical hernia at POD2	Untreated ACR for 5 months, chronic rejection, pneumonia	12.7	Exitus at 12.7 mo with COVID-19 related pneumonia before re-transplant
9	LLS/240	14.2	Mother	Hepaticojejunostomy	Jejunal perforation at POM1	Mild macrosteatosis	7.9	Alive with normal liver function on cycA
10	MS/150	7	Father	Hepaticojejunostomy	Iliac artery thrombosis	Sepsis, DIC	0.4	Exitus at 0.4 mo with sepsis
11	Reduced LLS/190	6.5	Mother	Hepaticojejunostomy	-	Initial poor function, sepsis, encephalopathy, tracheostomy-ventilator need	4.4	Exitus at 4.4 mo with an unknown reason
12	RL/680	72	Mother	Duct-to-duct	-	ACR at POD7, refractory ascites	3	Alive with normal liver function on tacrolimus and MMF
13	LLS/335	20	Father	Duct-to-duct	-	ACR at POW6	2.2	Alive with normal liver function on normal diet and tacrolimus and MMF

G: *Grams,* ***Kg:*** *Kilograms,* ***POM:*** *Postoperative month,* ***POW:*** *Postoperative week,* ***POD:*** *Postoperative day,* ***DIC:*** *Disseminated intravascular coagulation,* ***ACR:*** *Acute cellular rejection,* ***GIS:*** *Gastrointestinal system,* ***MMF=*** *Mycophenolate mofetil,* ***cycA=*** *Cyclosporin A.*

transplantation and untreated rejection due to social problems followed by severe COVID-19 related pneumonia caused loss of 3 patients with 62.5% survival in PFIC group.

There is a certain advantage of early liver transplantation especially LDLT for PFIC-2 patients because of very early presentation and rapid progression. However, unlike in PFIC2, early transplantation in PFIC1 is controversial. There are different outcomes in the literature although liver transplantation supposedly reverses the disease symptoms since it corrects the FIC1 gene in the liver. Post-transplant unfavorable outcomes for PFIC-1 were reported as worsening of extra-hepatic manifestations of the disease like diarrhea and short stature. Therefore, medical and surgical treatment preferences such as cholestyramine and biliary diversion should be considered for osmotic diarrhea caused by increased bile acids in the stool at pre- and post-transplant period for these patients. Hori et

al. (10) reported significant post-transplant hepato-steatosis in 8 out of 11 (72%) PFIC-1 patients with liver transplantation and 4 patients developed cirrhosis. Digestive symptoms were described in 90.9% of the patients. The 5-, 10- and 15-years patient survival rates were 90.9%, 72.7% and 54.5% respectively. Several studies reported specific gene mutations in some PFIC-1 patients which were associated with unremitting diarrhea, steatohepatitis and progressive fibrosis (8-16). These serious post-transplant complications need to be addressed well to decide best timing of the liver transplantation and genetic work-up in PFIC-1 patients for better management and outcomes. We had one child with PFIC-2 who was diagnosed at age of 11 months. He was 43 months-old and his body weight was 11 kg at time of consultation with decompensated cirrhosis in severe sepsis and intubated in PICU. Patient underwent LDLT after resolution of sepsis when he was still in PICU. He was discharged 51 days after transplant with good allograft function. In our series we had one patient with PFIC-1 and 3 patients with no subtype identification and none of these patients presented extrahepatic manifestations.

Liver transplantation is indicated for 20%-30% of Alagille syndrome patients because of intractable pruritis, cholestatic cirrhosis and associated complications including pruritis related poor quality of life over their lifespan (1). AS patients may have history of portoenterostomy mistakenly with the presence of early infancy prolonged conjugated hyperbilirubinemia and referred as biliary atresia for LT when liver biopsy shows just bile duct proliferation and if there are no obvious dysmorphic features (17-22). In our series one patient presented as biliary atresia with history of Kasai portoenterostomy and pathology of explanted liver made the accurate diagnosis as AS. Decompensated cirrhosis was the main indication for liver transplant with severe pruritis.

Alagille syndrome is a multisystem disorder with high incidence of cardiac and vascular anomalies, renal involvement with low glomerular filtration rate, ocular problems, skeletal fractures, and presence of facial dysmorphic features. These comorbidities might also complicate the post-transplant period and most of the patient deaths occur within 1st month due to multisystem participation. Kamath et al. (20) reported the median survival rate as 79% from all published literature ranging between 71% and 100%. The most important determinant for survival was described as associated cardiac anomalies varying from asymptomatic peripheral pulmonary stenosis to more complex midline defects and tetralogy of Fallot. Therefore, pre-transplant cardiac evaluation and attention to possible aggravation of extra-hepatic disease are very important concerns for the management of this patient group. Nephrotoxicity with calcineurin inhibitors, increased bone damage by steroid use and dyslipidemia and atherosclerosis caused by sirolimus should be considered during post-transplant follow up (17-22). In our series cardiac examination, echocardiographic and CT scan findings of all three patients revealed no cardiac or vascular abnormality. One patient presented dysmorphic facial figures with no other deformity. One patient had poor initial allograft function, encephalopathy and severe respiratory problems. This patient was followed by intermittent plasmapheresis sessions and transferred to her home country tracheostomy and ventilator dependent with request of the family. Death of the patient was reported within a month after departure. Living related donors should be well evaluated prior to the operation since they might be affected by JAG1 disease with no clinical features. Kasahara et al. (22) reported results from 20 AS patients stating comparable 80% 1-year survival rate with non-living donor LT outcomes. Authors addressed the importance of donor liver biopsy for possible duct hypoplasia and need for complete radiological vascular assessment for vascular anomalies including mid-aortic syndrome (22-23). We perform triphasic CT scan complete cardiac evaluation for living donors and there was no vascular abnormality in parent donors.

Tyrosinemia type-1 is an autosomal recessive metabolic disorder present in 2 forms as acute form in neonatal period or chronic form with development of HCC risk beside toxic effects of tyrosine and phenylalanine metabolites (1, 3-5,24-27). Hepatocellular carcinoma risk is very high in chronic form. The combination of diet with phenyl alanine and tyrosine-restriction and NTBC [2-(2-nitro-trifluoromethyibenzoyl)-1,3-cyclohexenedione] use which blocks the toxic metabolite formation is currently the first line treatment. Acute liver failure not responding to one-week treatment with NTBC, severe dysplasia or localized HCC, appearance of a new nodule and/or rebound in AFP levels under NTBC are considered as main indications for liver transplantation. The monitorization of nodules and AFP levels might be an option but it may increase the risk of recurrent HCC after transplantation. The starting time of NTBC is often used to distinguish the malignancy risk. Two years of age is referred as threshold, but HCC has been reported under 2 years. Dietary restriction related poor quality of life under NTBC is also a rare indication for LT. Heterozygous living donor parents can be used safely since they are not affected by the disease. LT does not completely correct the metabolic abnormalities because of the excretion of succinyl acetone by affected kidneys prior to NTBC use. Currently, renal impairment and indication of combined liver-kidney transplantation are not that much significant compared to the era before introduction of NTBC. Patients show normal liver function and normal growth on unrestricted diet with no metabolic crises after LT with patient survival rate higher than 85% (24-27). In our experience, one chronic form TT-1 patient was transplanted because of dysplastic nodules and high AFP levels from a parental donor. Patient was diagnosed at 11 months old and was on diet and NTBC treatment with no renal impairment.

Glycogen storage disease (GSD) types I, III, IV, VI, and IX are inherited glycogen metabolism disorders associated with

distortion of liver parenchyma including nodular formations and cirrhosis. Liver transplantation indication because of long-term complications despite good metabolic control with dietary adjustments including continuous nocturnal drip feeding to avoid fasting hypoglycemia and medical treatments such as allopurinol for hyperuricemia, ACE-I for proteinuria, and GCSF for neutropenia in GSD type-Ib. HCC has been reported in early adulthood within pre-existing hepatic adenomas in GSD type I, IV and VI (1,3,28-37). Life threatening cardiac complications in type-IIIa and renal impairment in type-Ia are also well-established problems. It is very important to achieve good plasma glucose control before and during the transplantation. LT corrects the primary enzyme defect in the liver with great success of patient and graft survivals, but extra-hepatic manifestations may still complicate the post-transplant period including renal disease progression in type-Ia and cardiomyopathy and skeletal myopathy in type-IIIa. Transplanted patients also state overall improvement in quality of life which is another very important consideration for need of LT in this group of disease (28-37).

In our series one patient with GSD-I was transplanted with no subtype identification. Patient was diagnosed with liver biopsy in her country at 9 months of age with dysmorphic facial figures and no extra-hepatic manifestation. Explanted liver showed cholestatic cirrhosis.

CONCLUSIONS

Liver transplantation is a lifesaving treatment for patients with PFIC, Alagille syndrome, tyrosinemia and GSD in the progression of these disorders due to liver failure, malignancies, and associated complications despite several medical and surgical treatment modalities. Especially LDLT is the ultimate choice for populations with very low organ donation rates and for early onset and rapidly progressing inherited disorders. Early diagnosis and liver transplantation before severe decompensation of end-stage liver disease is very crucial for successful outcomes.

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