DOI: 10.4274/jpr.82713

Original Article

Pediatric Liver Transplantation Outcomes for Metabolic and Nonmetabolic Diseases in Turkey: A Single Center Experience

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ABSTRACT

Aim: Liver transplantation (LT) is performed for several indications in the pediatric population, including malignancy and acute hepatic failure among others. LT has become an important treatment alternative for metabolic diseases. In most pediatric transplant centers, metabolic liver disease is the second most common indication for liver transplantation after biliary atresia. Our studies aim is to compare the post-transplant outcomes of the patients with metabolic and other liver diseases in our transplant program.

Materials and Methods: One hundred eighty-nine patients who underwent liver transplantation between 1997 and 2015 due to metabolic diseases and acute or chronic liver failure were included in the study.

Results: We enrolled 189 patients in our study. 54% (n = 102) male and 46% (n = 87) female patients were included in the study. Metabolic disease group include 56 patients. Progressive familial intrahepatic cholestasis (PFIC) is the most common disease among metabolic diseases resulting in LT Wilson disease takes second place. Post-transplant immunosuppression was similar for both groups. Although there was no difference in both groups, regarding onset of the post-transplant complications for graft type, recipient age. Biliary and portal vein complications were most particularly defined in the group with nonmetabolic diseases. There was no significant difference in survival between the two groups.

Conclusion: Liver transplantation is an important treatment option for acute hepatic failure and end-stage liver diseases. In addition, liver transplantation is an alternative treatment option for some metabolic diseases.

Keywords: Complications, non-metabolic diseases, metabolic diseases, liver, survival, transplantation

Introduction

In children, liver transplantation can be performed at many indications, including malignancy and acute hepatic failure. Liver transplantation is an important treatment option, especially in children with biliary atresia, progressive familial intrahepatic cholestasis (PFIC), Wilson Disease and some metabolic diseases (1,2). In metabolic diseases, multiorgan failure may occur due to accumulation of toxic metabolites in organs. In inherited metabolic diseases, liver

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Received: *13.03.2018* **Accepted:** *15.10.2018*

transplantation has two main purposes: to keep the patient alive in progression to hepatic failure and to completely eliminate the underlying metabolic defect for some metabolic diseases. Some metabolic disorders cause progressive liver damage and may require liver transplantation leading to liver failure (3). Other metabolic disorders do not cause structural liver damage, but toxic metabolites have extra hepatic effects in some diseases such as urea cycle defects, primary hypercalcemia type 1, and Crigler-Najjar Syndrome type 1 (CNS1). (3,4,5,6). Liver transplantation can be performed to relieve the enzyme deficiency if alternative treatment options are not sufficient or metabolic decompensation could not be prevent in metabolic diseases (3,7). Last few decades, LT become an alternative treatment in metabolic diseases. In most pediatric transplant centers, metabolic liver disease is the second most common indication for liver transplantation after biliary atresia (8, 9).

Due to the progress in the field, long-term survival rates of pediatric LT are now over 80 % with the majority of mortalities occurring within 6 months of the transplant procedure (10, 11). The survival rates for 1 and 5 years after liver transplantation in children are 77-86%, 73% and 87%, respectively (12, 13, 14). These rates may be better for children with liver transplantation for metabolic diseases. The 1- and 5-year survival rates of children with liver transplantation due to metabolic disease vary between 87-94%, 79% and 92%, respectively (15, 16, 17). The purpose of this study is to compare the treatment and follow-up results of patients with liver transplantation for metabolic disease and other causes in our transplantation program.

Materials and Methods

One hundred eighty-nine patients who underwent liver transplantation between 1997 and 2015 due to metabolic diseases and acute or chronic liver failure were included in the study. This retrospective study reviewed the records of the patients. After the liver transplantation, all the recipients were followed monthly during the first six months, every three months in the latter six months and after the first year they were followed up in every six months.

Gender, age, age at transplantation and type of transplantation, type of donor, rejection and complications were evaluated. The study was prepared in accordance with the Helsinki Declaration. Informed consent form was obtained from the patients' relatives.

Statistical Analysis

Results were expressed as mean values where indicated; a paired Student t-test was used to assess differences between the two groups. The Kaplan–Meier method was used to assess patient survival rates. Differences in survival were compared using a log-rank analysis. $P<0.05$ was considered significant. All the statistical analyses were performed using MedCalcx Software (Ostend, Belgium, https: medcalc.org; 2013) version 12.7.7.

Results

Total 189 patients, 54% (n = 102) of male and 46% (n = 87) of female were included in the study. Fifty-six patients in Metabolic disease group were enrolled (PFIC- 22, Wilson disease- 11, tyrosinemia type 1- 9, familial hyperlipidemia- 4, alpha 1 antitrypsin deficiency- 3, glycogen storage disease (GSD) type I- 3, Crigler Najjar syndrome type 1- 2, GSD type III- 1, GSD type IV-1 patients) the study. Details were given in figure 1. In non-metabolic liver disease group; there is 133 patients (biliary atresia-55, autoimmune hepatitis- 13, fulminant hepatitis- 32, tumor- 10, other cholestatic disease- 19 and others-4 patients). The diagnosis of this patients is detailed in figure 2.

Biliary atresia is the most common transplant indication for liver transplantation. The other important indications for liver transplantation are fulminant hepatic failure, autoimmune hepatitis and cholestatic liver diseases.

In total of 189 patients; 29.6% (n=56) of cases were diagnosed as metabolic diseases including Wilson disease, Tyrosinemia and PFIC. Median age at the diagnosis was 11.8 (1-31) months in non-metabolic groups and 2.2 (5 mounts- 17 years) years in the metabolic group. In metabolic diseases

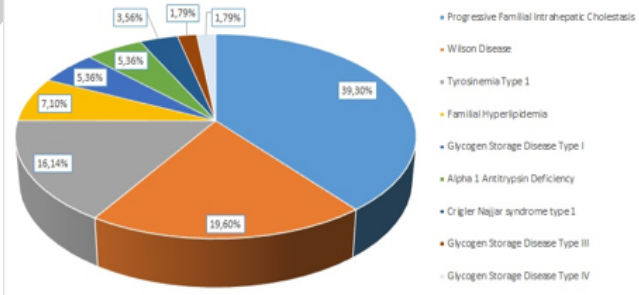

Figure 1. Metabolic diseases groups

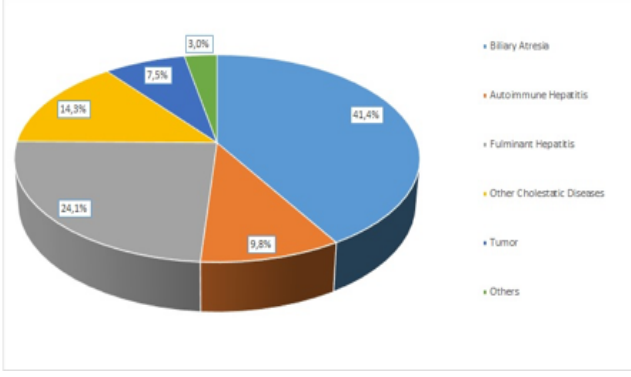

Figure 2. Non metabolic diseases groups

group, mean age at transplantation was 5. 52 ± 4. 75 (6 mounts- 17 years) years and non-metabolic group mean age at transplantation was 5. 6 ± 5. 4 (6 mounts-14 years) years. Characteristics of the patients diagnosed with nonmetabolic and metabolic diseases are shown in table 1. Characteristics of the patients diagnosed with Metabolic diseases are shown in table 2.

Only one patient with familial hyperlipidemia and one patient with PFIC were retransplanted. In the group of patients with metabolic diseases (n=56), 5 cases diagnosis with tyrosinemia type 1 who had developed hepatocellular carcinoma (HCC). PFIC was the most common disease in between metabolic diseases which ended up with LT, however the Wilson disease was the runner-up. In non-metabolic groups, 69.8% (n=92) patients were transplanted from living donors, whereas the rest of patients (n=41) were transplanted from cadavers. More than two-thirds of patients with metabolic disease had liver transplantation from live donors. Rejection was found in 15% of the patients with metabolic disease while the percentage of organ rejection in the other group was 18%. Post-transplant immunosuppression was similar for both groups. Although there was no difference in both groups, regarding onset of the post-transplant complications, graft type, recipient age. Biliary and portal vein complications were most particularly defined in the group with non-metabolic diseases. There were three patients with gastrointestinal system complications in the metabolic diseases group infect that no patient developed gastrointestinal complications in non-metabolic disease group. Post-transplant complications of the patients diagnosed with metabolic diseases were given in Table 3.

The rate of immunosuppressive drugs which were for liver transplantation due to metabolic disease vary as 60.7% tacrolimus, 28.5% sirolimus and 10.8% cyclosporine. The rate of immunosuppressive drugs which were for liver transplantation due to non-metabolic disease vary as , 71.4% tacrolimus, 18% cyclosporine and 9.8% sirolimus. For the other group, 71.4% tacrolimus, 18% cyclosporine and 9.8% sirolimus were used for liver transplantation. In terms of ongoing medication, no statistically significant difference was detected between two groups.

In non-metabolic disease group, the survival rate for the first year after transplantation was 82%, but in the fifth year this rate dropped to 79%; In the group of patients with metabolic disease, the survival rate after one year of transplantation was 80%, while in the fifth year it was 77% (Figure 3). No significant difference was detected between two groups.

Table I. Characteristics of the patients diagnosed with nonmetabolic and metabolic disorders

Group	Nonmetabolic disease	Metabolic disease	p
Number of patients			
Gender (F/M)	64/69	30/26	0.96
Mean age at transplantation	5.6±5.4	5.52±4.75	0.92
Donor type -Cadaveric -Living donor	 40 93	 19 37	0.90
Rejection	31	5	0.44
Treatment Siklosporin Tacrolimus Sirolimus	 24 95 14	 16 36 4	0.38
Number of patients with postransplant complications (%)	38 (28.6)	15 (26.7)	0.56

M: Male, F: Female

Table II. Characteristics of the patients diagnosed with metabolic disorders

	CNS Type1	GSD T-III	Wilson disease	PFIC	Alpha 1 antitrypsin deficiency	GSD Type-I	GSD Type-IV	Tyrosinemia	Hyperlipidemia
Number of patients	2	1	11	22	3	3	1	9	4
Number of alive patients	2	1	8	15	3	3	1	8	4
Median Age (year)	2	4	12.44±4.04	3.9±2.64	0.8±0.28	8.3±4.93	4	2.75±2.41	5.5±3.5
Donor type numbers Cadaveric/ Alive	1/1	-/1	5/6	8/14	-/3	1/2	-/1	1/8	-/4

GSD: Glycogen storage disease, CNS Type I: Crigler-Najjar syndrome Type I, PFIC: Progressive familial intrahepatic cholestasis

Discussion

This study reviewed the experience and long term follow up of the pediatric patients with metabolic and non-metabolic diseases who underwent liver transplantation at our center during the last 18 years. In the literature post transplantation survival rates of patients who had inborn errors of metabolism, appear to be higher, when it was compared to survival following transplantation for other indications, such as extrahepatic biliary atresia, acute liver failure, and post necrotic liver cirrhosis (16). Most studies regarding LT for metabolic liver diseases involve pediatric patients. In our study the survival rate for the first year after transplantation was 82%, but in the fifth year this rate dropped to 79%; in the group of patients with metabolic disease, the survival rate after one year of transplantation was 80%, while in the fifth year it was 77%. According to our analysis patient survival was similar to transplanted children for metabolic and non-metabolic diseases. Survival rate was same in both groups, which might be related to accompanied pre-transplant and post-transplant factors and the diseases, which caused parenchymal liver disease in both groups. Pre-transplant health status affects post-transplant survival (2). The one- and five-year patient survival rates were reported as between 92% and 94% in the United States (18) whereas Sze et al (19) were reported the survival 91%, 86%, respectively, in the United Kingdom. The survival rates at 1, 5, and 10 years in these studies were similar to other studies. (16, 17, 20).

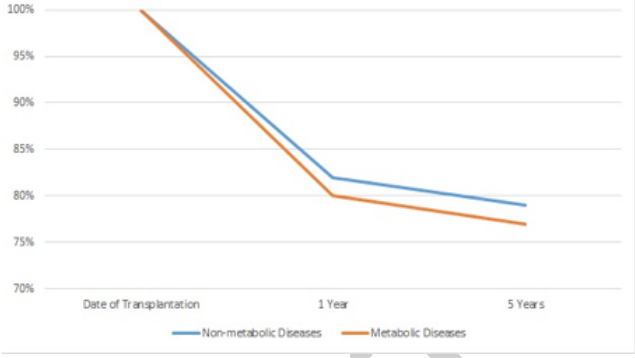

Figure 3. Survival rate of metabolic and non-metabolic diseases

Arnon et al (21) showed that survival rates of their patients with metabolic and non-metabolic diseases were 94.6 % and 90.7% at one year respectively and 88.9% and 86.1% respectively at five year. The cumulative survival rates in the pediatric patients with non-metabolic disease were 91.9%, 87.2%, and 85.8% at one, five, and 10 years, respectively (22). Survival rate was lower in both metabolic and non-metabolic disease group in our study, which was different from Kyler and his friends' study (15). Kyler et al. (15) and Arnon et al. (21) had patients without metabolic disease due to parenchymal liver disease, which may be due to a lower survival rate in our study. However, we had more patients with PFIC and Wilson Disease than other studies. Kyler et al (15) conspicuously consisted a lot of patients with alpha 1 antitrypsin deficiency (n: 261). However, Kyler et al (17) defined the metabolic group as only patients with biliary atresia, which meant that he compared the biliary atresia to non-metabolic group. These results may be due to the involvement of patients with liver transplantation due to tumor, autoimmune hepatitis, fulminant hepatitis, which might worsen the outcomes compared with postoperative transplantation due to BA. (23, 24). We classified the patients with PFIC into metabolic disease group, that's why survival rate is lower than other studies.

In our work, in accordance with other studies we found that PELD scores were lower in children with metabolic diseases, statistically significant (25). As a result of very good survival rates, complications after liver transplantation can be

Table III. Post-transplant complications of the patients diagnosed with metabolic diseases

	CNS Type 1	GSD Type III	Wilson disease	PFIC	Alpha 1 antitrypsin deficiency	GSD Type-I	GSD Type-IV	Tyrosinemia	Familial Hyperlipidemia
Number of patients	2	1	11	22	3	3	1	9	4
Biliary complications		1	5	2				-	
Renal Stone				-		1		-	
Portal Thrombosis				1				-	
HLH				1				-	
CRF				1		1		-	
OIH				1			1	-	

CRF: Chronic renal failure, OIH: Autoimmune hemolytic anemia, HLH: Hemophagocytic lympho histiocytosis, GSD: Glycogen storage disease, CNS Type I: Crigler-Najjar syndrome Type I, PFIC: Progressive familial intrahepatic cholestasis

seen in children. In Arnon et al study (21), gastrointestinal and hematological complications were more frequent. Peeters et al (1) reported less gastrointestinal complications post-LT in patients with metabolic disease than in those with BA, also. In our study, autoimmune hemolytic anemia is more common in patients with metabolic disease after transplantation than in non-metabolic disease. Gastrointestinal complications are more common in patients with transplants due to non-metabolic liver diseases (1). According to Kshara et al (24), seizure was one of the common problems, which could be related with type of metabolic disease. Effects on systems were different from each other in metabolic diseases. In our study we did not detected seizure after liver transplantation.

In terms of acute rejection rates, we found approximately 15 %, whereas Rosencrantz et al (25) found approximately 22 %, which was more than ours. This fact could be related to different treatment procedures. On our study, 61 % patients were on tacrolimus treatment.

The present study has several limitations that are the result of its single-center, retrospective design. In our study, biliary complications were the most common cause of the post-transplant complications in both groups, the latter was portal vein complications. The reason, which caused the difference from results of the other studies, might be due to the low cadaver rates, especially among child cadavers, and the tendency to prefer living donors for liver transplantation in our country.

Conclusion

In hereditary metabolic diseases, orthotopic liver transplantation causes very good survival outcomes. These children should be carefully monitored for the timing of transplantation. LT is one of the curative treatments in hepatic failure and end stage of liver failure. Also, we want to mention that, LT is alternative treatment in some metabolic diseases.

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