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Research

Outcomes of Pediatric Liver Transplantation in Inherited Metabolic Diseases: A Single-center's Experience

Kalıtsal Metabolik Hastalıklarda Pediatrik Karaciğer Nakli Sonuçları: Tek Merkez Deneyimi

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ABSTRACT

Objective: To expand on the hitherto limited knowledge of the indications and outcomes of pediatric liver transplantation (LT) for inherited metabolic diseases (IMDs).

Methods: Demographic data, pretransplant clinical and laboratory profiles, post-transplant outcomes and survival rates of twelve patients under 18 years who underwent LT for IMDs between January 2015 and June 2021 were analyzed.

Results: Twelve (6 female) of 104 (11.5%) patients had a diagnosis of IMD. Four of the patients were diagnosed with primary hyperoxaluria type 1; two had Crigler-Najjar syndrome; and there was one patient each having maple syrup urine disease, propionic acidemia, tyrosinemia type 1, glycogen storage disease type 1a, Wilson's disease, and homozygous familial hypercholesterolemia, respectively. The mean current ages and ages at transplantation of the patients were 8.7 (1-14.2) and 6.5 (0.3-12.8) years, respectively. Their mean follow-up time was 2.7 (0.5-6.1) years. The distribution of LT indications was poor metabolic control (42%), the need for frequent hospitalization due to an acute life-threatening attack (17%), progressive neuromotor retardation (8%), and target organ failure (33%) respectively. The mean time between diagnosis and LT was 2.7 (0.5-6.1) years. No neurological, hematological, or metabolic complications were observed after LT. The biliary stricture developed in two (16.7%) patients, separation of arterial anastomosis in one (8.3%) and ascites infection in one (8.3%) patient. One-year patient and graft survival rates were both 100%. A significant difference was observed between the patients' pre-operative and current height and weight standard deviation scores, respectively (p=0.001 and p=0.006).

Conclusion: LT is a good therapeutic option for improving the metabolic control and quality of life of patients with IMDs. Survival rates are excellent compared with other LT indications when appropriate timing and indication is adhered to.

Keywords: Intensive care, metabolic diseases, pediatric surgery

ÖZ

Amaç: Kalıtsal metabolik hastalıklar (KMH) için pediatrik karaciğer nakil (KN) endikasyonları ve sonuçları hakkında şimdiye kadar sınırlı olan bilgileri genişletmektir.

Gereç ve Yöntem: Ocak 2015 ile Haziran 2021 arasında KMH nedeniyle karaciğer nakli yapılan 18 yaş altı on iki hastanın demografik verileri, nakil öncesi klinik ve laboratuvar profilleri, nakil sonrası sonuçları ve sağkalım oranları analiz edildi.

Bulgular: One hundred four (%11,5) hastanın 12'si (6 kız) KMH tanısı aldı. Hastaların dördü primer hiperoksalüri tip 1 tanısı aldı. İkisinde Crigler-Najjar sendromu, sırasıyla akçaağaç şurubu idrar hastalığı, propiyonik asidemi, tirozinemi tip 1, glikojen depo hastalığı tip 1a, Wilson hastalığı ve homozigot ailesel hiperkolesterolemi tanılı birer hasta vardı. Hastaların ortalama güncel yaşları ve nakil sırasındaki yaşları sırasıyla 8,7 (1-14,2) ve 6,5 (0,3-12,8) yıl idi. Ortalama takip süreleri 2,7 (0,5-6,1) yıldı. KN endikasyonlarının dağılımı kötü metabolik kontrol (%42), akut yaşamı tehdit eden atak nedeniyle sık hastaneye yatış ihtiyacı (%17), ilerleyici nöromotor gerilik (%8) ve hedef organ yetmezliği (%33) idi. Tanı ile KN arasındaki

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ortalama süre 2,7 (0,5-6,1) yıldı. KN sonrası nörolojik, hematolojik veya metabolik komplikasyon gözlenmedi. İki hastada (%16,7) biliyer darlık, bir hastada (%8,3) arteriyel anastomoz ayrılması ve bir hastada (%8,3) asit enfeksiyonu gelişti. Bir yıllık hasta ve greft sağkalım oranları %100 idi. Hastaların ameliyat öncesi ve mevcut boy ve kilo standart sapma skorları arasında sırasıyla anlamlı fark gözlendi (p=0,001 ve p=0,006).

Sonuç: KN, KMH olan hastalarda metabolik kontrolü ve yaşam kalitesini iyileştirmek için iyi bir tedavi seçeneğidir. Sağkalım oranları, uygun zamanlama ve endikasyonda diğer nakil endikasyonlarına kıyasla daha yüz güldürücüdür.

Anahtar Kelimeler: Yoğun bakım, kalıtsal metabolik hastalıklar, pediatrik cerrahi

INTRODUCTION

Since the first pediatric liver transplantation (LT) was performed in the USA in 1967 and subsequently in Europe in 1968, survival rates have increased with further development of surgical techniques, use of effective new immunosuppressants, and improved postoperative care (1).

Moreover, indications for LT have expanded over time, and inherited metabolic diseases (IMDs) have become one of the leading indications. IMDs are a group of diseases that impair the function of metabolic pathways that result in severe multi-system dysfunction or death. Although rare as individual entities, collectively these diseases occur with considerable frequency, represent the second most common indication for LT after biliary atresia (2). Today, IMDs constitute approximately 20% of pediatric LT indications (3,4). Nowadays, increasing use of next generation sequencing diagnostic methods has already made it possible to identify the fact that IMDs underlie some of the cryptogenic causes (5). LT in IMDs was first performed successfully in a case of tyrosinemia type 1 (TT1) in 1978, and then in a case of ornithine transcarbamylase deficiency in 1989, and, with an increasing number of examples and new indications, it has become an important treatment modality looking toward the future (6).

LT in IMD is mainly performed for two reasons: primary liver diseases (acute liver failure, cirrhosis, malignancy, cholestasis, steatosis) caused by IMDs, which directly affect the liver parenchyma, and secondly due to cases where permanent enzyme replacement therapy is provided in IMDs due to deficiency of enzymes synthesized by liver cells (7) (Table 1).

Despite disease-based indications having been determined, patient-based criteria should also be evaluated in IMDs: 1) failure to respond to medical treatment; 2) need for frequent hospitalization due to an acute life-threatening attack; 3) poor quality of life; 4) progressive neuromotor retardation due to poor metabolic control; 5) growth retardation; 6) laboratory tests that do not improve (ammonia, lactate, cholesterol, etc.); 7) presence or risk of malignancy; and 8) acute liver failure. Before making the LT decision, patients should be evaluated in terms of all these risks and evaluated on an individual-patient basis.

In some cases, LT alone is not enough to replace the missing enzyme. Dual transplantation is needed to prevent insufficiency in the other target organs. Liver-kidney transplantation is the most common combination practice in IMDs. Indications for combined liver-kidney transplantation were primary hyperoxaluria type 1 (PH1), methylmalonic aciduria, glycogen storage disease type 1, and those presenting with or at risk of end-stage renal disease.

We reported our center's experience of pediatric liver and liver-kidney transplantation for IMDs.

METHODS

Patients diagnosed with IMD, <18 years of age, who received a liver-only, or combined liver-kidney transplant participated in the study after providing their consent. Patient and donor demographics, patients' preoperative and postoperative clinical and laboratory data, and post-transplant outcomes were recorded from medical records, and the laboratory results were retrieved electronically from the hospital database. Patient survival and graft survival rates, immunosuppression and concomitant medications were specified. Additionally, preoperative and postoperative growth and neurological status of the patients was compared.

Ethical Statement

This study was prepared in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (2000). Furthermore, it was approved by the Acibadem University Ethics Committee (decision no: 2021-24/01, date: 17.12.2021).

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0. Categorical variables were defined as frequency and percentage rate, and numerical variables were determined as mean ± standard deviation (SD). Student's t-test was performed for normally-distributed numerical variables. Statistically-significant results were defined as those with a p-value of <0.05.

Table 1. Indications for liver transplantation in inherited metabolic diseases

IMDs of primary hepatic origin without parenchymal liver damage	IMDs of primary hepatic origin with parenchymal liver damage
Urea cycle disorders (excluding ASL)	Genetic cholestasis syndromes (PFIC, Alagille syndromes)
Organic acidemias (propionic acidemia, methylmalonic acidemia)	Wilson's disease
Crigler-Najjar syndrome	Hereditary hemochromatosis
Atypical hemolytic uremic syndrome (cobalamin metabolism disorders)	Tyrosinemia type 1
Primary hyperoxaluria type 1	α-1-antitrypsin deficiency
Maple syrup urine disease	Argininosuccinic aciduria
Acute intermittent porphyria	GSD type 1 (adenoma/hepatocellular carcinoma)
Glycogen storage disease type 1a	Lysosomal acid lipase deficiency
Homozygous familial hypercholesterolemia	Mitochondrial depletion syndromes

ASL: Argininosuccinate lyase, PFIC: Progressive familial intrahepatic cholestasis, IMD: Inherited metabolic disease, GSD: Glycogen storage disease

RESULTS

A total of 104 patients underwent liver-only and combined liver-kidney transplantation in our center between November 2015 and January 2021. Twelve of the total (11.5%) had underlying causes of IMDs. Four of the patients were diagnosed with PH1, two with Crigler-Najjar syndrome, and one patient each respectively with maple syrup urine disease (MSUD), propionic acidemia, TT1, glycogen storage disease (GSD) type 1, Wilson's disease, and homozygous familial hypercholesterolemia (HFH) (Figure 1).

All patients had living-donor LT. All donors were first-degree relatives of the patients. Combined liver-kidney transplantation was performed in four patients with PH1. The demographics of the patients and donors are summarized in Table 2.

The distribution of LT indications was determined as poor metabolic control (n=5, 42%), the need for frequent hospitalization due to an acute life-threatening attack (n=2, 17%), progressive neuromotor retardation (n=1, 8%) and target organ failure (n=4, 33%) respectively (Figure 2). The preoperative clinical and laboratory data of the patients have been summarized in Table 3.

The mean length of stay in the pediatric intensive care unit and the total duration of hospital stay post-LT were six days (range: 3-15) and 27.7 days (range: 9 to 71) respectively. Tacrolimus was used as the first-choice drug; only one patient was switched to cyclosporine due to tacrolimus's side effect of renal toxicity. IMD-specific treatment was given for an average of four days post-operatively (range: 2-8). Branched-chain amino acids (leucine, valine, isoleucine) in MSUD and tyrosine levels in TT1 returned to the normal range on the eighth postoperative day. In propionic acidemia, urinary metabolites returned to the normal ranges within an average of 14 days (±3.45 SD) (Figure 3a-3b). On the 3rd and 7th postoperative days, toxic amino acid levels in aminoacidopathies; blood ammonia and glutamine levels in organic acidemia were evaluated. According to these

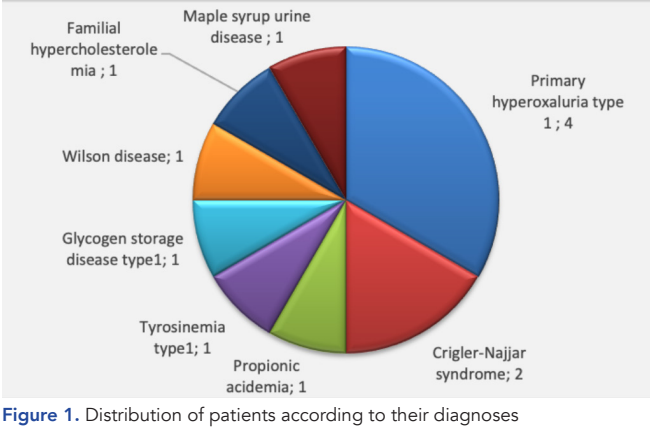

Figure 1. Distribution of patients according to their diagnoses

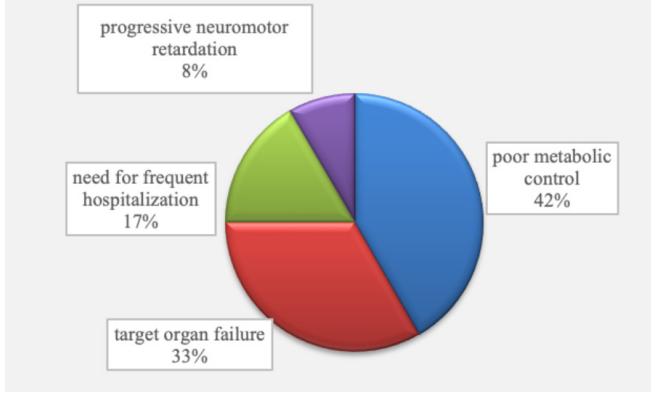

Figure 2. The distribution of patient-based LT indications of the patients
LT: Liver transplantation

levels, protein restriction diet of the patients was reduced and than stopped. None of the patients continued on a protein-restricted diet. Anti-oxidant treatment (coenzyme Q-10, B complex, L-carnitine) of the patient diagnosed with propionic acidemia was continued for one year; and the patient with a diagnosis of TT1 continued to use nitisinone at a low, renal-protective dose.

No neurological, hematological, renal, or metabolic complications were observed in the short-term (≤1 month) postoperative follow-up of any patient, but ascites infection developed in one (8.3%) patient. With respect to long-term surgical complications (>1 month), partial obstruction of the biliary stricture was observed in two (16.7%) cases, and the artery anastomosis separation was seen in one patient (8.3%). Total short-term and long-term complication rates were 8.3% and 25%, respectively. All were reversible and no permanent complications occurred.

The median follow-up period of the patients was 2.5 years (0.5-6.1) and their 1-year patient and graft survival rates were both 100%. (It is impossible to give a 5-year survival rate yet, since the average follow-up period is <5 years.). For the same period, the overall survival rate of all pediatric LT in our center was 94.6%.

A significant difference was observed between pre-operative and current height and weight SDs of the patients (p=0.001 and p=0.006). The MSUD patient with moderate mental retardation remained stable, and the patients with mild mental retardation suffering from propionic acidemia and GSD type 1 showed neurocognitive improvement. All patients were completely cured of metabolic disease.

DISCUSSION

The data of twelve pediatric patients who underwent LT for IMDs, which comprised 11.5% of all LTs, from November 2015 to January 2021 were reported.

Since most enzymes in metabolic pathways are synthesized within the liver, LT is a life-saving procedure and improves

Table 2. Demographics of the patients and the donors

Mean current age (yrs) (min-max)	8.7 (1-14.2)
Mean age at transplantation (yrs) (min-max)	6.5 (0.3-12.8)
Gender (F/M)	6/6
Consanguinity n (%)	9 (81)
Mean time between diagnosis and Tx (yrs) (min-max)	4.2 (0.8-11)
Mean follow-up time (yrs) (min-max)	2.7 (0.5-6.1)
Mean age of donors at transplantation (min-max)	34.2 (21-50)
Gender of donors (F/M)	8/4

F: Female, M: Male, Tx: Transplantation, yrs: Years, min: Minimum, max: Maximum

Table 3. Clinical and laboratory data of patients before transplantation

PELD score	15.1 (5-28)
Elective/Emergency ratio	10/1
Height (SDS)	-0.05 (-2.3- 1.2)
Weight (SDS)	-0.12 (-2.6- 0.9)
Neurological involvement, n (%)	2 (18)
Renal involvement, n (%)	5 (45)
Cardiac pathology, n (%)	1 (8)
Metabolic decompensation	0 (0)
Preop CRRT	3 (27)
INR	1.26 (0.9-2.3)
Albumin (g/dL)	3.14 (2.3-4.6)
Total bilirubin (mg/dL)	7.23 (0.23-28.24)

CRRT: Continuous renal replacement therapy, INR: International normalized ratio, PELD: Pediatric end-stage liver disease, SDS: Standard deviation score

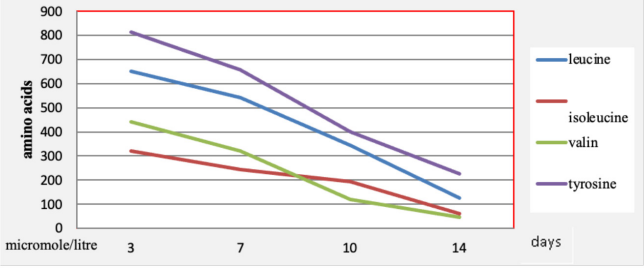

Figure 3a. Postoperative plasma amino acid levels of MSUD and TT1 patients

MSUD: Maple syrup urine disease
TT1: Tyrosinemia type 1

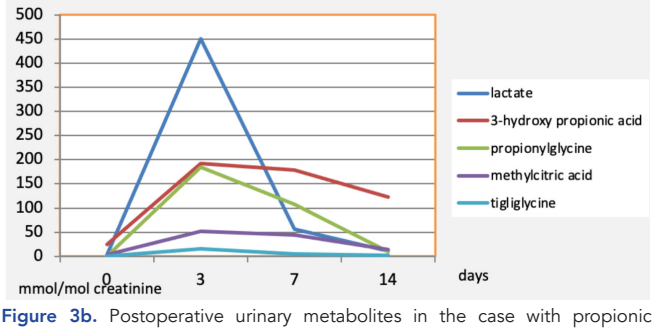

Figure 3b. Postoperative urinary metabolites in the case with propionic acidemia

quality of life in IMDs. As well as preventing liver damage caused by IMDs, it is considered a type of gene transfer which is based on the idea of transferring a genetically-normal liver to correct metabolic imbalances. In this context, poor metabolic control and the need for frequent hospitalizations, which constituted 69% of the total indications, were the leading indications in our study. Target organ failure ranks second among the causes, accounting for 33% of total indications.

We can divide IMDs into two groups according to their post-transplant status: patients who are completely cured and do not need additional metabolic therapy and follow-up; and patients whose metabolic follow-up is continued due to failure to correct enzyme deficiencies in other tissues (8). Our study group consisted of patients who were completely cured.

Overall, the reported patient survival and graft survival at 1 year were 97.3% and 96.6% respectively; 5-year patient survival varied from 88.9-92%, and in terms of graft survival this figure was 83.8% for cases of pediatric LT due to all IMDs (3,9). These rates are higher than those for other indications of LT. In our IMD case series, 1-year survival rates were found to be similar, and as high as has been reported in the literature. This situation is associated with normal liver parenchyma and liver function of LTs performed due to IMDs.

The most common post-LT complications are re-operation (31.7%), hepatic artery thrombosis (6.3%), and portal vein thrombosis (3.2%) over the short-term; and biliary tract complications (13.6%) over the long-term, which were reported by the society of pediatric LT (3). Biliary complications were seen at a similar rate (16.7%), but vascular complications (8.3%) were less common in this study group.

MSUD is caused by decreased activity of the branched-chain alpha-ketoacid dehydrogenase complex, the second enzymatic step in the degradative pathway of the branched-chain amino acids (BCAAs-leucine, isoleucine, and valine). LT is a curative treatment method option for MSUD, which is characterized by high mortality and morbidity due to attacks with a rapid increase in BCAAs (10). A leucine-restricted diet forms the basis of medical therapy. Poor metabolic control and frequent attacks are the most common causes for requiring LT. Our patient was transplanted on the basis of these indications and, post-LT leucine and other BCAAs rapidly decreased to normal levels. The neuromotor development of the patient, without a new metabolic attack, improved. Patients suffering from MSUD, which is one of the IMDs that cause serious mortality and morbidity due to severe metabolic attacks at all ages, should be recommended for LT at the earliest appropriate time.

TT1 is caused by a deficiency of fumarylacetoacetase, the final enzyme of the tyrosine degradation pathway. It is characterized by progressive liver disease and secondary renal tubular dysfunction leading to hypophosphataemic rickets. Medical treatment is following a combination of a tyrosine-restricted diet and nitisinone, a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase to prevent the formation of the toxic substances maleylacetoacetate and fumarylacetoacetate, and their saturated derivatives. LT in TT1 provides a curative treatment with excellent results in experienced centers (11). The indications are (1) failure to respond to primary medical treatment, including diet and nitisinone; (2) acute hepatic failure unresponsive to medical treatment; (3) malignancy: a) hepatocellular carcinoma (HCC), b) liver with nodular cirrhosis (very high risk of developing HCC), c) rising or abnormal alpha-fetoprotein (AFP); and (4) chronic liver/kidney failure, respectively. LT was performed in our patient due to a progressive increase in AFP levels, but no macroscopic HCC was detected. Although we stopped a tyrosine-phenylalanine-restricted diet in this patient, we continued low-dose nitisinone treatment to prevent renal involvement. It seems that close monitoring of AFP level and renal function should be ensured in TT1, and transplantation should be prioritized in cases with persistent AFP elevations.

GSD1a is caused by glucose-6-phosphatase deficiency, characterized by severe hypoglycemia during the first year of life and hepatomegaly caused by accumulating glycogen. Uncooked corn-starch alternating with frequent meals high in complex carbohydrates in daytimes and continuous nocturnal infusion form the basis of medical therapy. Despite good medical treatment, patients may develop liver and kidney failure and severely stunted growth (12). Hepatic adenomas with potential for malignant transformation represent a further indication for LT. According to the metabolic status of the patient, the indication for a liver-only or a combined liver-kidney transplantation is determined. Single organ transplants are preferred because the risk of complications increases in combined transplants. However, liver-only transplant patients should have their kidney function closely monitored (13).

Propionic acidemia is an organic acidemia caused by a deficiency of mitochondrial propionyl CoA carboxylase, resulting in the accumulation of propionic acid metabolites, and dysfunction in both the electron transport chain and urea cycle pathways. It can cause liver, kidney and heart

failure, and severe neuromotor retardation due to the effects of other pathways. Therefore, the risk of developing post-LT complications and mortality is higher compared to other IMDs (14). The overall mortality rate post-LT in PA has been reported at around 30%, which is signficantly higher than for other indications (10-20%) (15,16). The biliary stricture developed in our patient, who recovered following PTC. Post-LT diet and medical treatments were continued for an average of one week. Additionally, anti-oxidant therapy was given for one year for neurocognitive support. In this way, our patient progressed through his developmental stages, and he started walking without support.

PH1 is an inherited metabolic disorder characterized by a deficiency of the liver-specific alanine-glyoxylate aminotransferase, resulting in the overproduction of oxalate and end-stage renal disease: combined liver-kidney transplantation is the best treatment for patients with PH1 with end-stage renal disease (17). Most our IMD patients were PH1 patients who underwent combined kidney-liver transplant. Although there is an increased risk compared with LT-alone, experienced, and multi-disciplinary approaches, and good postoperative care led to excellent results in all patients (18). The renal function of the patients was also stable at their most recent evaluation. Patient survival in PH1 at 2, 5, 10, and 15 years was 87.5%, 87.5%, 78%, and 78% respectively (19). Although it is a small series, the one-year survival for our patients is 100%.

Wilson disease is a multi-systemic IMD causing acute and chronic liver failure. Medical treatments can effectively remedy and protect liver and non-hepatic tissues. LT is offered when the Dhawan score is ≥11 (as this predicts a mortality of greater than 97%) or where there is no response to medical therapies (20,21). Post-LT survival for Wilson disease is excellent with a 5-year survival of up to 90% (22).

HFH is an autosomal dominant disorder that has mortal cardiovascular effects even in pediatric age groups. Medical and dietary therapies have limited effects on patients undergoing lipid apheresis to decrease low-density lipoprotein cholesterol (LDL-C). Since LDL receptors are mainly located in the liver, LT is considered as the only way to correct hepatic cholesterol metabolism (23). After LT, LDL-C rapidly falls below 180 mg/dL. Cardiovascular disease risk is significantly reduced and post-transplant survival rates are also promising in transplanted HFH patients.

Crigler-Najjar syndrome is an autosomal recessive IMD, caused by UDP-glucuronosyltransferase and characterized by high levels of unconjugated hyperbilirubinemia leading to brain damage and even death (24,25). Although it is classified under the group of IMDs of primary hepatic origin without parenchymal liver damage, detection of fibrosis in liver tissue in recent publications is an interesting development, representing new information (26). The cause of the fibrosis and tissue damage is unknown. Phototherapy (12 hours/day), despite being highly effective in the first few years after birth, is socially inconvenient and becomes less effective in older age groups. LT is the only the curative treatment (25). In some study groups, while the outcome was excellent with a patient survival rate of 100%, the graft survival rate was not good (61.5%) (26). Re-transplantation in Crigler-Najjar syndrome is relatively more common compared to other indications for LT. The reason for this situation has not been fully elucidated. Our two patients showed normal neuromotor development without impairment of their activities of daily living or education.

In our study, it was shown that LT performed timely and for the correct indication not only prevented organ damage in IMDs, but also safeguarded the physical and neurological development of patients. Rapid rectification of surgical and medical complications has increased the preference for LT as a treatment due to increased patient survival.

Study Limitations

Although IMDs are in the rare disease group, the small sample size is the limitation of the study.

CONCLUSION

LT is a good therapeutic option for improving the metabolic control and quality of life in cases of IMD. While the risk of complications is less in IMD-induced LTs, their survival rate is better than in other indications.

Acknowledgments: We would like to thank the patients and family members who participated in this study.

ETHICS

Ethics Committee Approval: This study was approved by the Acibadem University Ethics Committee (decision no: 2021-24/01, date: 17.12.2021).

Informed Consent: Written consent was obtained from the participants.

Authorship Contributions

Surgical and Medical Practices: M.E., V.E., G.Ş., A.Ç., S.K., R.E., Concept: M.E., V.E., Design: M.E., V.E., Data Collection or Processing: M.E., V.E., Analysis or Interpretation: M.E., V.E., Writing: M.E, V.E., S.K., R.E.

Conflicts of interest: The authors declare that they have no conflict of interest.

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