DOI: 10.59213/TP.2023.36025
Trends in Pediatrics 2023;4(4):227-237

Review

Liver transplantation in pediatric monogenic metabolic diseases

Fatma İlknur Varol

Department of Pediatric Gastroenterology and Hepatology, Inonu University Faculty of Medicine, Malatya, Türkiye

Cite this article as: Varol Fİ. Liver transplantation in pediatric monogenic metabolic diseases. Trends in Pediatrics 2023;4(4):227-237.

ABSTRACT

Monogenic diseases are the results of a single gene mutation leading to alterations or defects in a single enzyme causing severe metabolic derangements causing multi-systemic systemic disease and even death Current management strategies include diet to reduce the accumulation of metabolic waste products and treatment to increase the excretion of the toxic metabolites and to induce the activity of the mutant enzyme. However, liver transplantation is the only therapeutic strategy that offers a chance of cure to children with certain genetic diseases.

Keywords: Liver transplantation, pediatric liver diseases, pediatric monogenic diseases

INTRODUCTION

Monogenic diseases are the results of a single gene mutation and are very rare diseases, occurring in 10 neonates per 1000 births according to the data of the World Health Organization.[1] Liver transplantation (LT) is the only therapeutic strategy that offers a chance of cure to children with certain genetic diseases. LT can significantly improve the quality of life of pediatric patients who suffer from congenital metabolic diseases. Advances in patient care, surgical technique, post-transplant surgical care, and immunosuppression have resulted in a 95% postoperative survival rate in the first year and 85% in the 5th year following liver transplantation.[2] In 1978, for the first time, a patient with tyrosinemia was transplanted for the first time which was followed by a liver transplantation for ornithine transcarbamylase (OTC) deficiency in 1989. These two events were evolutionary because LT became the new hope for the treatment of patients with monogenic diseases.[3,4]

Monogenic diseases are the results of single gene mutation causing alteration or defect in a single enzyme causing severe metabolic derangements causing multi-systemic systemic disease and even death. Currently, the strategies of management include diet to reduce the accumulation of metabolic waste products and treatment to increase the excretion of the toxic metabolites and to induce the activity of the mutant enzyme. The patients have to comply with a strict diet and have the risk of decompensation with every infectious process that is encountered. LT is the only means of cure that can provide a better quality of life for these patients.[5]

There are many monogenic diseases of the amino acid, lipid, and elemental metal metabolism; as well as mitochondrial disorders that can be cured by LT. According to the data of the study group for pediatric liver transplant (SPLIT) between 1995 and 2008 446 pediatric transplants were performed and 14.9%of these procedures were performed for metabolic liver diseases. Urea cycle disorders (UCD), the most common metabolic disease requiring liver transplantation, accounted for 25.6% of patients with metabolic diseases. Other frequent metabolic diseases that require liver transplantation are α-1anti-trypsin deficiency (19.7%), cystic fibrosis (10%), Wilson's Disease (7.6%),

Correspondence: Fatma İlknur Varol **E-mail:** drivarol@yahoo.com
Received: 04.08.2023 **Accepted:** 10.11.2023

tyrosinemia (7.4%), maple syrup urine disease (MSUD) (6.5%), glycogen storage disease (GSD) (5.2%) and miscellaneous minor diseases (17.2%).[6]

The donors of these patients are usually the parents who are also the carriers of these autosomal recessive diseases. The data regarding living-related liver transplantation from heterozygous donors have been limited. Kasahara and colleagues have analyzed the Japanese Transplant registry and more than 95% of the donors were carriers for the monogenic diseases of the recipients. The most common disease reported in this cohort was Wilson's disease (30.4%). This was followed by OTC (20.6%), methylmalonic acidurias (MMA) (10.3%), GSD (7.7%), tyrosinemia (6.7%), propionic acidemia (4.6%), and primary hyperoxaluria (4.6%). The long term survival and better results were observed in Wilson's disease and UCD. In OTC, female donor candidates who were asymptomatic should be evaluated with thorough metabolic evaluation. Female donor candidates who are symptomatic should be excluded from donor evaluation.[7] The risk-benefit assessment should be performed with great care and a follow-up of the recipients in the postoperative period should be performed with great care. The monogenic diseases that are treated with liver transplantation are divided into two classes: those that cause liver parenchymal damage and those that do not cause any liver parenchymal damage (Table 1).

I-Monogenic Diseases that Cause Liver Parenchymal Damage

Ia) Hereditary Tyrosinemia Type 1

This is an autosomal recessive disease that is caused by fumarylacetoacetate hydrolase (FAH) deficiency in the liver and kidneys. Usually, it presents as a multisystemic disease with a mild elevation of transaminases during infancy together with severe coagulopathy. In older children and adults it can present itself as chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). Associated components of the disease can be hypertrophic cardiomyopathy, renal tubulopathy, neuropathy, and porphyria-like symptoms. Pathognomonic biochemical changes are hypertyrosinemia, hypermethioninemia, elevated blood and urine succinyl acetone, and elevated serum alpha-fetoprotein.[5] The indications for liver transplantation are progressive liver disease despite phenylalanine and tyrosine restricted diet and 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) (NTBC) treatment, alpha-fetoprotein elevation during NTBC treatment, solitary hepatic nodule with a diameter greater than 10 mm or increase in the size and number of hepatic nodules or confirmation of HCC during follow-up.[5,8] Data from the United Network for Organ Sharing (UNOS) database suggests that 1- and 5 -year survival following LT for Hereditary Tyrosinemia Type 1 is 90.4% and 90.4%, respectively. The 1- and 5-year graft survival following LT is reported to be 78.1-84.4% and 63.3%-75.2%. Graft survival rates increased over time with advances in surgical and postoperative care, including immunosuppressive treatment.[9]

Acute metabolic decompensation is very rare in hereditary tyrosinemia type 1; however, fasting and catabolism associated with surgery may adversely affect the liver functions and may exacerbate porphyria-like episodes in patients. Therefore, it is recommended that preoperative fasting should be minimized and that patients be continuously infused with 10% dextrose solution. In the post-transplant period, succinyl acetone can still be detected in the serum and urine of the patients. Urinary succinyl acetone levels should be monitored in the post-transplant period due to the risk of tubulopathy; on the other hand, NTBC treatment is not recommended.[5]

Ib) Wilson's Disease

Wilson's disease is a congenital autosomal recessive disease which is characterized by a mutation in ATP7B, which encodes an intracellular transmembrane copper transporter. This results in abnormal copper accumulation in various tissues and results in tissue damage due to copper-related toxicity.[10]

Table 1. Monogenic diseases that are treated with liver transplantation

Diseases with Parenchymal Liver Damage	Diseases without Parenchymal Liver Damage
Hereditary Tyrosinemia Type I	Urea Cycle Defects
Wilson's Disease	Organic Acidemia
Alagille Syndrome	Defects of Fatty Acid Oxidation Pathway
Progressive Familial Intrahepatic Cholestasis	Primary Hyperoxaluria Type I
Disorders of Bile Acid Synthesis	Mitochondrial Hepatopathy and Systemic Mitochondrial Disease
Alfa-1 Antitrypsin Deficiency	Crigler-Najjar Type I
Glycogen Storage Disease	Acute Intermittent Porphyria
Cystic Fibrosis	Factor VII Deficiency
Ductal Plate Malformations	Protein C Deficiency
Erythropoietic Protoporphyria	

Wilson's disease-related end-stage liver disease can present as different disease spectrums which can be summarized as acute liver failure, acute/chronic hepatitis, cirrhosis, portal hypertension.[11] Copper chelating agents or zinc sulfate are used to prevent copper absorption from the gastrointestinal tract. Acute liver failure, chronic liver disease unresponsive to treatment and decompensated cirrhosis are the main indications for LT in patients with Wilson's disease. In other liver diseases and acute liver failure, Nazer's Wilson Index can be used for the decision-making process for LT. The component of this index bilirubin, AST, white blood cell count and albumin; and any patient with a score > 7 suggests proceeding with liver transplantation because the mortality without intervention is high. The sensitivity and specificity of this scoring system in predicting LT are 93% and 98%, respectively.[12] The efficacy of LT in patients with neuropsychiatric symptoms is controversial. The pathophysiology of neuro-Wilson includes tissue damage due to copper elimination, and it can be hypothesized that reversal of the process by LT can prevent further tissue damage and promote timely recovery of neural tissue. This hypothesis has been supported by various studies.[13,14] On the other hand, it has been shown that the existing central nervous system damage and cerebral dysfunction do not recover sooner than 6 months following the transplant procedure.[5] It has been reported that full recovery is possible in 56-77% of the cases. On the contrary, there are reports that suggest a worsening of the neuropsychiatric symptoms following transplant procedure, and it is known that patients with neuropsychiatric symptoms have lower survival rates than patients with isolated liver failure. For this reason, in patients who present with combined liver failure and neuropsychiatric symptoms require thorough neurologic and psychiatric evaluation before the decision to proceed with liver transplantation is made.[1,5] Specific metabolic follow-up is not required in these patients in the post-transplant period, and the medical management strategy is the same as in the patients without any metabolic defect.[5] The 1- and 5-year survival rates of the patients with Wilson's disease following liver transplantation are 91.9% and 88.2%, respectively.[15]

Ic) Alagille Syndrome

Alagille syndrome is a congenital autosomal dominant multisystemic disease that primarily affects the liver and the heart of the individuals. The main diagnostic criteria of Alagille syndrome are chronic cholestasis, congenital malformations of the heart, vascular system, eyes, and the kidneys along with a characteristic facial morphology. Severe cholestasis, intractable pruritus, growth retardation, hypercholesterolemia and osteodystrophy are some of the complications of the disease that can be reversed by LT.[16] Before the transplant procedure, patients should be thoroughly evaluated for extrahepatic manifestations of the disease, and the vascular system should be evaluated by imaging studies for cerebral aneurysm, carotid artery stenosis, coarctation of the abdominal aorta, and renal artery stenosis. Any vascular anomaly should be corrected before the liver transplantation. Patients with complications such as intractable pruritus and deformed xanthoma which are not life-threatening, non-transplant surgical alternatives such as biliary diversion or ileal bypass should also be considered.[8] Current series in the literature show that the median survival following liver transplantation is 79%. Early experience with liver transplantation for Alagille syndrome showed a 1-year survival of 57%; however, current high-volume studies suggest that 1-year survival of the patients following liver transplantation ranges from 71 to 100%.[17] In 2019, Valamparampil and colleagues reported the results of their study showing 100% patient and graft survival rates during a median of 32 (3-72) months follow-up period in patients with Alagille syndrome who underwent liver transplantation.[18]

Id) Progressive Familial Intrahepatic Cholestasis

Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of autosomal recessive diseases that cause cholestasis and liver failure. It has many subtypes that result from different genetic mutations. PFIC type 1 results from a mutation in the ATP8B1 gene. Typically, there is severe cholestasis in the early years of infancy together with normal serum gamma-glutamyl transferase (GGT) levels. Associated symptoms may include chronic diarrhea and asthma-like respiratory complaints. Pathologic analysis may reveal giant cell transformation, canalicular cholestasis with biliary plugs, ductular degeneration, and structural lobular irregularities.[19] In PFIC type 1, partial external biliary diversion or ileal bypass can provide clinical, biochemical and histologic improvement along with prevention of disease progression and support for patient growth if it can be performed before the development of cirrhosis.[20] Progressive steatohepatitis that may lead to cirrhosis in liver allograft in the post-transplant period has been reported.[8]

PFIC type 2 results from a mutation in the ABCB11 gene that encodes BSEP. Similarly, serum GGT levels are normal and the patient has cholestasis. PFIC type 2 is a more rapidly progressing disease that presents with higher aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, cholelithiasis and giant cell hepatitis. Furthermore, there is a high risk of hepatocellular carcinoma. Giant cell hepatitis in pathologic analysis is typical for this disease.[19,21] In mild forms of the disease, ursodeoxycholic acid and biliary diversion may result in good clinical response. In contrast to PFIC type 1, a successful liver transplantation is curative in PFIC type 2.[8,20] However, auto-antibodies may develop against the mutant BSEP protein

encoded by the defective ABCB11 gene, which may result in cholestatic disease in the transplanted liver graft that may resemble the original disease in the native liver.[22] There is no specific treatment to prevent the recurrence of the disease after liver transplantation. However, studies have shown that Rituximab which is a chimeric monoclonal anti-CD20 antibody may be effective in preventing recurrences.[23]

PFIC type 3 develops as a result of a mutation in the ABCB4 gene, which encodes the MDR glycoprotein. Its clinical course is usually different from the previous two PFIC types that we have mentioned. Biochemically, the patients have high serum GGT levels. Usually, individuals carrying the heterozygous alleles of the ABSB4 gene present with transient neonatal cholestasis. However, the onset of the disease is usually in the late adolescence and early adulthood. Cholelithiasis, intrahepatic cholestasis of pregnancy, and drug-induced cholestasis may be seen during the course of the disease. The initial findings of the disease are jaundice, pruritus and the biochemical signs of the liver failure. Pathologic analysis shows mild giant cell hepatitis, portal fibrosis and proliferation of the biliary canaliculi.[19] Treatment with ursodeoxycholic acid usually results in clinical and biochemical recovery; however, 15% of patients do not respond to treatment and the disease progresses rapidly. In patients who do not respond to medical therapy, LT can be considered for the treatment of the disease.[8,24]

PFIC type for is a congenital autosomal recessive disease that results from a mutation in the TJP2 gene. Liver failure is prominent, and develops early, and progresses rapidly. Patients usually need liver transplantation in the first few years after birth. There have been reports of the hepatocellular carcinoma development on initial admission of the patients. Extrahepatic manifestations of the disease may involve the nervous and respiratory system of the patients.[25] The GGT levels are usually normal in these patients. Histopathologic analysis shows giant cell transformation and intracellular cholestasis is also common.[19,21]

PFIC type 5 is an autosomal recessive disease resulting from a mutation in the NR1H4 gene that encoding FXR. The disease presents early in infancy and children have normal GT levels and severe cholestasis. In addition, the liver enzymes are normal but serum bile acids and alpha-feto-protein levels are elevated. Patients have vit K-independent coagulopathy and hyperammonemia. Liver failure develops very rapidly and progresses to end-stage liver failure that requires liver transplantation. Pathological analysis shows hepatocellular ballooning, giant cell transformation and micronodular cirrhosis.[19,21]

The mutation in the MYO5B gene results in microvillus inclusion disease and can also present as isolated liver disease.[19,21] Patients present around the first year of life with low serum GGT, cholestasis, hepatomegaly, and normal or elevated serum transaminases. Histopathologic analysis shows giant cell transformation, hepatocellular damage, portal and lobular fibrosis.[19]

Currently, LT offers the only means of cure for PFIC-related end-stage liver disease. However, LT may worsen the extrahepatic manifestations of PFIC type 1. The recipients who have PFIC type 2 may have recurrence of the disease in the liver allograft and the postoperative surveillance of these patients are mandatory and the immunosuppressive treatment should be given with great care.[26] A recent meta-analysis showed that a total of 131 patients from all subtypes had a graft and patient survival rate of 76.6% and 85.2%, respectively; and the longest follow-up period was 19 years.[27]

Ie) Defects of Bile Acid Synthesis

This spectrum of disease usually presents as neonatal cholestasis or hepatitis. However, it may also present as chronic liver disease in older children. Usually, the serum bile acid levels are normal or low, serum GGT levels are normal and pruritus is not observed in this disease, which is quite different from other cholestatic diseases of the liver. Usually, administration of cholic acid and chenodeoxycholic acid is effective in treating patients, if the disease is diagnosed early. LT is indicated in patients in whom the disease has progressed and end-stage liver disease has developed.[8,28]

If) Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin (AAT) is a protease inhibitor found in the serum of healthy individuals and it protects the tissue from neutrophil-derived proteases such as elastase.[5,29] The presentation of AAT-related liver disease is highly variable. Generally, AAT rarely presents as a rapidly progressive, lethal liver disease that requires liver transplantation in early infancy. PiZZ is a severe form of AAT that has an autosomal co-dominant trait. Seven percent of the affected individuals have long-term obstructive jaundice, and 80% of the patients do not exhibit signs of chronic liver disease until the age of 18. Hepatocellular carcinoma may develop in children with AAT-related cirrhosis.[8,30] Pulmonary involvement is prominent, and even though liver functions improve following liver transplantation, pulmonary functions continue to deteriorate.[5,31] For this reason, strict monitoring of the pulmonary system after liver transplantation is mandatory even in patients with normal preoperative pulmonary functions.[5] The 1-, 3-, 5-, and 10- year overall survival

rates of the patients following liver transplantation are 90%, 88%, 85%, and 78%, respectively.[31]

Ig) Glycogen Storage Disease

The most common indication for LT among inborn errors of carbohydrate metabolism are the Glycogen Storge Diseases (GSD). It is a spectrum of diseases caused by defects in the enzymes that take part in glycogen synthesis, breakdown, or glycolysis, and the presentation of the disease may be isolated liver involvement, isolated muscle involvement, or involvement of both.[5] The enzymes of glycogen metabolism are present in many organ systems and tissues. For this reason, the extent of extrahepatic manifestations varies from one patient to other. Liver transplantation is frequently performed in patients with GSD types I, II, and IV.[32] Poor metabolic control, multiple adenomas, and/or suspicion of hepatocellular cancer in GSD type I; poor metabolic control, progressive liver failure or presence of complicated cirrhosis or suspicion of hepatic malignancy in GSD types III and IV are the main indications for LT in this spectrum of disease.[8]

GSD type I accounts for 25% of the cases and LT is therapeutic in a selected group of patients. GSD type Ia is also known as the von Gierke disease, is caused by defects in glucose-6-phosphatase and glucose-6-phosphorylase enzyme complex, mainly affects the liver and the kidneys.[33] It is the most common variant of GSD type I. Glucose-6-phosphorylase deficiency in GSD type Ia causes severe hypoglycemia, lactic acidosis, hypertriglyceridemia, uric acidemia, hepatomegaly, “doll’s face” and failure to thrive. One of the most common complications observed during adolescence is the development of hepatic adenomas.[5] In GSD type Ib, symptoms resemble those of GSD type Ia, in addition to neutropenia and inflammatory bowel disease. Dietary modification can normalize the blood glucose levels and reduce the lactic acid levels in patients with GSD type Ia. In patients with GSD type Ia with poor metabolic and biochemical control or in patients with large hepatic adenomas that cannot be resected, LT may be a therapeutic option. Indications for LT in GSD type Ib are similar, but also includes recurrent infections due to neutropenia.[34] Important perioperative concerns in GSD type I are lactic acidosis and hypoglycemia. Stress-induced lactic acidosis may be life-threatening. Surgical stress may lead to a severe lactic acidosis which may cause multiple organ failure and death.[5] The stress-induced hormones and glucose-6-phosphate accumulation due to the metabolic defect cause a robust of glycogenolysis and the glycolysis is induced, which causes an excess of lactic acid production. To prevent hypoglycemia and lactic acidosis, it is recommended that the preoperative fasting period should be minimized, and dextrose infusion should be started at rate of 4-9 mg/kg/min adjusted according to the age of the patient.[5,35] Intraoperatively, close monitoring of glucose, lactate and pH is required and the dextrose infusion rates should be carefully adjusted especially during hepatic dissection and anhepatic phase in order to achieve glycemic control in the patients. Infusion solutions live lactated ringer should be avoided because of the lactate content. In patients with lactic acidosis, sodium bicarbonate infusion is required to correct the deficit. Results from a cohort of 80 patients with GSD type I who received LT showed that metabolic control and tolerance to fasting improved after the transplant procedure.[34] LT reverses the liver dysfunction, growth retardation, and neutropenia. LT was also shown to cure the inflammatory bowel disease in patients with GSD type Ib. However, it is recommended that strict surveillance should be performed for neutropenia, neutrophil dysfunction, and inflammatory bowel disease in the postoperative period.[35] GSD type I is associated with progressive renal disease; and unfortunately, LT cannot reverse the progression of the renal disease. For this reason, renal functions should be monitored regularly after LT.[5]

Ih) Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease that is cause by a mutation in the CFTR gene, which encodes a transmembrane conductance regulator protein.[36] Only 35% of the patients with CF present with a liver disease. However, 5-10% of the patients with liver disease develop cirrhosis.[37] LT for CF constitute 3.5% of the transplants performed in the pediatric age group.[38] Esophageal variceal bleeding is the most prominent component of the presentation of end-stage liver disease due to CF. Recurrent episodes of variceal bleeding are indications for LT.[38] Furthermore, the biliary cirrhosis that develops in these patients may lead to accumulation of ascites and may compromise the respiratory dynamics of the patients. The optimal timing of LT depends on the suitability of cardiopulmonary functions, the presence of active acute or chronic infection, and the nutritional status of the patient. LT should be performed before the forced expiratory volume in first second (FEV 1) decreases below 50%.[39] The presence of certain microbial agents in the respiratory tract of individuals is a complex and a controversial subject in patients with CF for whom LT is being considered as a treatment option. The presence of *Aspergillus species* in the sputum of the individual is not a contraindication to LT.[38] However, colonization of the respiratory tract with resistant strains of *Pseudomonas Aeruginosa* or *Burkholderia Cepacian* is a risk factor for the development of lethal postoperative infections. The presence of these resistant strains is considered an absolute contraindication to LT by many experienced transplant centers. LT should not be performed in patients with active lung disease. The contraindications for LT in patients with CF are (i) presence of a long-term history of recurrent intermittent pulmonary infections

that compromise pulmonary functions, (ii) colonization of the respiratory tract with Burkholderia Cepacia and other resistant microbial organisms, (iii) high resting partial carbon dioxide pressure on arterial blood gas analysis, (iv) presence of extensive pulmonary fibrosis determined by imaging techniques, (v) presence of severe pulmonary fibrosis with right ventricular dysfunction. Satisfactory results have been obtained with combined lung-liver or heart-lung-liver transplantation in patients with CF-associated cirrhosis and severe pulmonary disease or pulmonary hypertension.[40]

LT should be performed early in the course of CF-related end-stage liver disease. Molmenti and colleagues[38] have analyzed the timing of LT in CF-related liver disease in pediatric patient; and their results suggest that the results of early LT led to better outcomes than the patients who waited longer before the transplant procedure. In patients who died, there was failure to thrive, poor nutritional status, severe pancreas exocrine insufficiency, and higher meconium ileus incidence.[38] The long-term survival rate after LT in patients with CF was reported to be around 75%. Pulmonary infections and sepsis are very lethal complications encountered after LT and the most common cause of mortality in the post-transplant period is the pulmonary complications in these patients. Pediatric patients have better survival when compared to adults.[40]

Ij) Ductal Plaque Malformations

In pediatric patients, this group of diseases includes autosomal recessive polycystic renal disease, Caroli disease, isolated hepatic fibrosis. LT is indicated in patients with recurrent cholangitis, biliary sepsis, portal hypertension causing hepatopulmonary syndrome or variceal bleeding. Treatment options include isolated LT, combined liver-kidney transplantation, and isolated renal transplantation. Isolated liver transplantation depends on the severity of renal failure in the patients.[8]

Ik) Erythropoietic protoporphyria

The most common form of porphyria is erythropoietic protoporphyria (EPP), which is caused by a defect in the activity of ferrochelatase (FECH), the enzyme in the last step of the heme biosynthesis.[41] Protoporphyrin is the precursor of porphyrin, and in patients with EPP, it starts to accumulate in the bone marrow and is then taken up by the liver. EPP causes edema of the skin, erythema; and occasionally, it can lead to severe photosensitivity characterized by tender vesicular and bullous lesions of the skin. In addition, in some patients, it can lead to severe protoporphyrin related liver failure that requires LT.[42] Although the first LT for EPP was reported in 1980, LT is not curative in this disease because protoporphyrin is continuously produced leading to liver allograft damage.[43,44] Bone marrow transplantation is required before LT to prevent the development of liver allograft dysfunction. Before LT, protoporphyria levels should be reduced by administration of intravenous hemin, plasma exchange, or ursodeoxycholic acid and cholestyramine treatment. Neuropathy has been reported after the transplant procedure and should be monitored closely because it may lead to pulmonary insufficiency and pulmonary functions should be supported in these patients following LT.[5] In the post-transplant period, 1-, 5-, 10-year survival rates are 77%, 66% and 66%, respectively. The recurrence rate of the disease in the liver allograft is reported to be 69%.[44]

II- Monogenic diseases that do not cause liver parenchymal damage

IIa) Urea Cycle Defects

The urea cycle is a vital pathway that produces urea as the end product of protein catabolism. It facilitates the detoxification and excretion of nitrogenous metabolites from the body.[5] Urea cycle defects (UCD) result from defect in major enzymes in the metabolic pathway that disrupt the detoxification of nitrogenous compounds and the synthesis of arginine synthesis. The major enzymes that are defective in UCD are carbamoyl phosphate synthetase 1 (CPS 1), ornithine transcarbamylase (OTC), arginosuccinate synthetase (ASS), arginosuccinate lyase and arginase 1 (ARG1). In this section, we will try to summarize the clinical and physiopathological characteristics of the functional defects of these enzymes. OTC deficiency is an X-linked trait, while others are autosomal recessive diseases. Clinical signs can be seen in any age group, but are frequently observed in the neonatal period of life. Typically, affected neonates present with decreased feeding, lethargy, nausea, and tachypnea starting from hours to days after birth. It progresses rapidly and may lead to death. Irreversible neurological damage can be seen in UCD and therefore, LT should be considered early in the evaluation of treatment options.[1,5,8] The goal of UCD treatment is to minimize ammonia production while maintaining the nitrogen balance. For this reason, dietary modification, control of plasma ammonia and arginine by administering sodium benzoate and sodium/glycerol phenylbutyrate, and supplementing essential amino acids are necessary in the management of these patients. Nevertheless, patients with UCD experience episodes of hyperammonemia crisis during the periods of catabolic stress.

In UCD, OTC deficiency is the most common indication for LT. LT has been successfully performed for citrullinemia, CPS1, arginosuccinate lyase, and argininemia deficiencies. In

patients with UCD, hyperammonemia episodes are completely cured following LT, and dietary protein restriction is no longer necessary after the transplant procedure.[45]

Heterozygous individuals can be living donors for LT in patients with UCD. Only in OTC, asymptomatic female donors can be living donors after through metabolic evaluation. Symptomatic females should not be evaluated as living donors.[45]

In the perioperative period, fasting and surgical stress may result in excessive protein catabolism and hyperammonemia. Strict surveillance of nitrogen balance is necessary in order to provide metabolic complications and associated morbidity in patients. Preoperative lipid solutions and glucose infusion and minimization of the fasting period are recommended. Hyperammonemia should be corrected and ammonia- excreting medication should be administered whenever necessary. Close monitoring of ammonia levels in the perioperative and postoperative periods is recommended to support metabolic balance in patients.[46]

In patients with OTC and CPS1 deficiency, extrahepatic citrulline is insufficient and monitorization of plasma citrulline level is recommended and any deficiency should be supplemented.[5] The 1- and 5- year survival rates of patients following LT for UCD are reported to be 97% and 89%, respectively.[47]

IIb) Organic Acidemia

This is a group of metabolic disorders in which the metabolism of amino acid (especially the branched-chain amino acids) is disrupted and there is an excessive accumulation of organic acids in the urine or blood of the individuals.[48] It is classified into 5 subtypes: branched-chain organic acidemia, multi-carboxylase deficiencies, glutaric acidemia, fatty acid oxidation defects, and inborn errors of energy metabolism. The most common forms of the disease are methylmalonic acidemia (MMA), propionic acidemia (PA), and isovaleric acidemia. Other forms of the organic acidemia are maple syrup urine disease (MSUD), homocystinuria, biotin-resistant 3-methylcrotonyl-CoA carboxylase deficiency, 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) lyase deficiency and ketothiolase deficiency and glutaric acidemia type I (GA I). The typical clinical presentation includes toxic encephalitis-related neurologic symptoms such as vomiting, reduced feeding and seizures, abnormal tonus and lethargy that can progress to coma. In older children, deterioration of intellectual function, ataxia, or other focal neurologic symptoms can be observed. Prolonged fasting can trigger a catabolic state that may exacerbate the metabolic crisis. Therefore, in patients with organic acidemia, if a procedure requiring fasting is planned, than the patients should be hospitalized and strict metabolic surveillance along with intravenous glucose infusion is recommended. LT may be considered in the treatment of patients with organic acidemia who have intractable hyperammonemia, failure to thrive, or severely reduced quality of life.[8]

In classic MMA and PA, the infants usually present with lethargy that can progress to coma or death, vomiting, metabolic acidosis, hyperammonemia, and encephalopathy. Medical and dietary modifications include protein restriction, supplementation of nutritional formulations, maintenance of acid base balance, carnitine supplementation, and antibiotic therapy to reduce enteric propionic bacteria. There is a continuous systemic production of toxic metabolites resulting in an inability to control the disease despite aggressive medical therapy. Typically, during the natural course of organic acidemia, metabolic decompensation can be seen during prolonged periods of catabolic stress, which may be life-threatening if the episodes are recurrent. Mental retardation, hypotonia, cardiomyopathy, pancreatitis, and osteopenia are common in PA. MMA has similar findings in addition to renal insufficiency. Patients remains at risk for progression of neurologic symptoms and progressive renal failure despite a successful liver transplantation.[1,5,8] In patients with MMA, serum MMA concentrations and the protein intolerance are corrected after LT, but not completely reversed. Dietary restriction should continue and strict monitorization of the toxic metabolites, acid/base balance, and the renal functions is recommended following LT. Renal dysfunction is progressive and central nervous system damage is irreversible once it develops; therefore, LT should be considered early in the course of the disease.[5]

MSUD is the result of a disorder of branched-chain amino acid (BCAA) metabolism. It is an autosomal recessive disease and the defective enzyme is branched-chain α-ketoacid dehydrogenase (BCKAD), which is the enzyme of the rate-limiting second step of branched-chain amino acids such as leucine, isoleucine, and valine. The affected infant has a sweet odor to the urine hence the name maple syrup urine disease has been given.[49] The affected individuals have neurocognitive deterioration and catabolic stress induces metabolic decompensation in the patients. Although, LT does not reverse the existing damage that has occurred, it reverses the metabolic effects and results in prevention of progression of neurological damage and reduces the need for protein restriction in the diet.[50,51]

Episodes of metabolic decompensation create a risk factor for the patients. For this reason, it is necessary to minimize the fasting period before surgery and monitorization of the serum leucine, acid/base balance, serum glucose, and fluid-electrolyte

levels.[52] Plasma BCAA can be monitored perioperatively; studies have shown that isoleucine levels have return to normal 6 hours after the liver transplant procedure. Nutritional support can be modified according to the serum levels of the BCAA.[5]

Since LT does not cure the underlying enzymatic defect, metabolic decompensation has been reported after liver transplantation under severe physiological stress.[51] The explanted liver of the patients with MSUD can be used for domino liver transplantation to non-MSUD recipients because the extrahepatic tissue of the recipient will have a fully functional enzyme and it will not create a potential risk.[1,5,8]

IIc) Defects of Fatty Acid Oxidation

Fatty acid oxidation is a critical energy supply for high energy-consuming tissues such as heart and skeletal muscle. Furthermore, it is the only metabolic pathway that supplies the necessary energy during the periods of fasting. Defects in the fatty acid oxidation pathway are a serious congenital disease that leads to hypoketotic hypoglycemia, acute encephalopathy, cardiomyopathy, rhabdomyolysis, metabolic acidosis, and disturbances in liver functions. Fever, nausea and vomiting, and prolonged fasting may lead to lethal complications. Hypoketotic hypoglycemia and symptoms resembling Reye syndrome can be seen in infancy, and this condition can persist through childhood and adolescence.[8] There may be recurrent episodes of acute liver failure. Dietary modification is the main treatment modality. Treatment of acute episodes includes infusion of 10 mg/kg/min to maintain the serum glucose levels above 100 mg/dl. Dietary modification reverses acute liver failure episodes and controls almost all the symptoms. Strict dietary modification can reduce the need for LT. Liver transplantation is the treatment of choice in patients with fulminant hepatic failure who are unresponsive to suitable dietary modification.[53]

IId) Primary Hyperoxaluria Type 1

Primary hyperoxaluria type 1 is an autosomal recessive metabolic disorder that results from a defect in a hepatic peroxisomal enzyme; alanine-glyoxylate aminotransferase which is encoded by the AGXT gene. Overproduction of oxalate and excessive urinary excretion causes recurrent nephrolithiasis, nephrocalcinosis, which may lead to end-stage renal failure. Accumulation of calcium oxalate can be seen in the blood vessels, retina, heart, peripheral nerves, bone and bone marrow and the synovial fluid. Liver is the organ that detoxifies glyoxylate and prevents calcium oxalate accumulation, for this reason LT is curative in these patients. Planning LT early in the course of the disease prevents progression of damage to the kidneys and other organs.[1,5,8] Patients with renal failure should receive combined liver-kidney transplantation. In patients with mild to moderate renal damage that does not require dialysis, isolated liver transplantation can be considered for the treatment of the metabolic disease.[54,55] If combined liver and renal transplantation is not possible, staged transplantation can be a therapeutic choice. Liver transplantation should be chosen as the first transplant procedure in patients with even minimal renal function. Heterozygous healthy living related donors can be chosen for partial liver transplantation and good results have been reported. Renal oxalate accumulation can be seen after combined liver-kidney transplantation, and a multidisciplinary approach is required for the management of these patients.[5]

IIe) Familial Hypercholesterolemia

Familial hypercholesterolemia is an autosomal dominant disease that caused by a mutation in the gene encoding the low-density lipoprotein (LDL) receptor. Hypercholesterolemia, atherosclerosis, and ischemic heart disease have been reported to present in childhood. Xanthomas are yellow skin lesions and are common in these patients. Mutations in *LDLR*, *APOB,* or *PCSK9* genes have been identified in patients with familial hypercholesterolemia. Patients with *LDLR* homozygous mutations have very high LDL levels, severe atherosclerosis that is unresponsive to standard anti-hyperlipidemic therapy.[56] Failure to control LDL levels with accurate medical therapy is an indication for LT. LT reverses the xanthoma and also, causes a rapid decline in the plasma LDL levels. Effective treatment with statins and treatment modalities such as plasmapheresis have significantly decreased the need for LT in hypercholesterolemia. Currently, hypercholesterolemia is a treatment option for individuals with homozygous *LDLR* mutations.[56,57]

Before LT, a comprehensive and thorough cardiac evaluation is required to assess the level of atherosclerosis. Coronary artery bypass surgery is required in patients with severe atherosclerosis. Liver transplantation early in the course can minimize the incidence of cardiovascular disease and is associated with better outcomes.[58]

The long-term effects of LT on cardiovascular diseases are not clear, and statin treatment continues despite a significant decrease in plasma LDL levels.[56,59] In patients with familial hypercholesterolemia and ischemic heart disease, combined liver-heat transplantation has excellent results.[60,61] Ten-year patient survival rates have been reported to exceed 70%.[62]

IIf) Mitochondrial Hepatopathies and Systemic Mitochondrial Diseases

Mitochondrial diseases are a spectrum of diseases that include acute liver failure, severe neuromuscular deficits, multiorgan involvement or isolated liver disease. Medical therapy includes coenzyme Q10 and a vitamin cocktail to support the electron transport chain. The effect of medical therapy on mitochondrial hepatopathy is undetermined.[63,64] The clinical characteristics of mitochondrial hepatopathies are well defined and there is no definitive treatment for these patients which leads to poor outcomes.[65,66] Currently, the role of LT in the treatment of mitochondrial hepatopathy is controversial. LT is not suitable for pediatric patients with severe extrahepatic mitochondrial disease with multiorgan involvement. Extrahepatic mitochondrial disease can develop after LT, and the relatives of the patients should be informed of this possibility.[8]

IIg) Crigler-Najjar Type I

Crigler-Najjar Type I syndrome is an autosomal recessive disease resulting from the deficiency of uridine diphosphate glucuronosyltransferase. It presents as unconjugated hyperbilirubinemia during infancy. The initial therapy of the patients aims at preventing kernicterus; and to achieve this, treatment options include exchange transfusion and long-term phototherapy. During hyperbilirubinemia crisis, the optimal duration of phototherapy is 20-24 hours. Furthermore, the optimal duration of phototherapy to maintain acceptable bilirubin levels is 8-12 hours. LT is the gold standard and the only treatment option before irreversible brain damage develops.[1,5,8] The reason for this is because of the fact that bilirubin levels normalize after LT and if LT can be performed before irreversible brain damage, neurological damage can be stopped and the existing deficits may be reversed.[5] It is important to maintain the bilirubin-albumin balance before liver transplantation and drugs that affect bilirubin and albumin conjugation should be avoided.

IIh) Acute Intermittent Porphyria

Acute intermittent porphyria (AIP) is a rare metabolic disorder including the heme biosynthesis. AIP results from the deficiency of the enzyme hydroxymethylbilane synthase (HMBS), which is also known as porphobilinogen deaminase (PBGD). Once the heme biosynthesis is disrupted, porphobilinogen starts to accumulate in the cytoplasm of the cells. Acute episodes are characterized by abdominal pain and tachycardia which are neurovisceral crises that are seen during the natural course of the disease. Treatment includes avoidance of agents that trigger the acute attacks. Treatment of the patients during the acute attacks includes hydration of the patients and administration of glucose and hemin. LT is therapeutic for patients with recurrent and lethal acute attacks. LT prevents the development of irreversible neurological damage.[5] Renal dysfunction is a common complication of AIP in the long term. Combined liver-kidney transplantation has been reported to be successful in these patients.[67-69] Renal dysfunction is very important for the perioperative period during LT. The transplant surgeons should be aware that the patients with AIP may have subtle renal dysfunction, and fluid-electrolyte balance and the blood pressure of the patients should be closely monitored.[5]

IIj) Factor VII Deficiency

Factor VII deficiency is treated with fresh frozen plasma, cryoprecipitate, and recombinant Factor VIIa.[8,70]

IIk) Protein C Deficiency

Purpura fulminans is the severe form of Protein C deficiency that is seen in the neonates and it is usually life-threatening. In older children, its clinical characteristics are heterogeneous. The risk of vascular thrombosis is high.[8,71] Medical therapy is usually the treatment of choice for both Protein C and Factor VII deficiencies. LT is indicated in patients with complications or in individuals whom the medical therapy option has failed.[8]

Author contribution

Concept: FİV; Design: FİV; Data Collection or processing: FİV; Analysis or interpretation: FİV; Literature Search: FİV; Writing: FİV. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Fagiuoli S, Daina E, D'Antiga L, Colledan M, Remuzzi G. Monogenic diseases that can be cured by liver transplantation. J Hepatol. 2013;59:595-612. [Crossref]
2. Rawal N, Yazigi N. Pediatric Liver Transplantation. Pediatr Clin North Am. 2017;64:677-84. [Crossref]
3. Largillière C, Houssin D, Gottrand F, et al. Liver transplantation for ornithine transcarbamylase deficiency in a girl. J Pediatr. 1989;115:415-7. [Crossref]
4. Mowat AP. Liver disorders in children: the indications for liver replacement in parenchymal and metabolic diseases. Transplant Proc. 1987;19:3236-41.
5. Oishi K, Arnon R, Wasserstein MP, Diaz GA. Liver transplantation for pediatric inherited metabolic disorders: Considerations for indications, complications, and perioperative management. Pediatr Transplant. 2016;20:756-69. [Crossref]
6. Arnon R, Kerkar N, Davis MK, Anand R, Yin W, González-Peralta RP; SPLIT Research Group. Liver transplantation in children with metabolic diseases: the studies of pediatric liver transplantation experience. Pediatr Transplant. 2010;14:796-805. [Crossref]
7. Kasahara M, Sakamoto S, Horikawa R, et al. Living donor liver transplantation for pediatric patients with metabolic disorders: the Japanese multicenter registry. Pediatr Transplant. 2014;18:6-15. [Crossref]
8. Squires RH, Ng V, Romero R, et al; American Association for the Study of Liver Diseases; American Society of Transplantation; North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2014;59:112-31. [Crossref]
9. Arnon R, Annunziato R, Miloh T, et al. Liver transplantation for hereditary tyrosinemia type I: analysis of the UNOS database. Pediatr Transplant. 2011;15:400-5. [Crossref]
10. Tanzi RE, Petrukhin K, Chernov I, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet. 1993;5:344-50. [Crossref]
11. European Association for Study of Liver . EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56:671-85. [Crossref]
12. Dhawan A, Taylor RM, Cheeseman P, De Silva P, Katsiyiannakis L, Mieli-Vergani G. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. Liver Transpl. 2005;11:441-8. [Crossref]
13. Stracciari A, Tempestini A, Borghi A, Guarino M. Effect of liver transplantation on neurological manifestations in Wilson disease. Arch Neurol. 2000;57:384-6. [Crossref]
14. Catana AM, Medici V. Liver transplantation for Wilson disease. World J Hepatol. 2012;4:5-10. [Crossref]
15. Garoufalia Z, Prodromidou A, Machairas N, et al. Liver Transplantation for Wilson's Disease in Non-adult Patients: A Systematic Review. Transplant Proc. 2019;51:443-5. [Crossref]
16. Englert C, Grabhorn E, Burdelski M, Ganschow R. Liver transplantation in children with Alagille syndrome: indications and outcome. Pediatr Transplant. 2006;10:154-8. [Crossref]
17. Kamath BM, Schwarz KB, Hadzić N. Alagille syndrome and liver transplantation. J Pediatr Gastroenterol Nutr. 2010;50:11-5. [Crossref]
18. Valamparampil JJ, Reddy MS, Shanmugam N, Vij M, Kanagavelu RG, Rela M. Living donor liver transplantation in Alagille syndrome-Single center experience from south Asia. Pediatr Transplant. 2019;23:e13579. [Crossref]
19. Henkel SA, Squires JH, Ayers M, Ganoza A, Mckiernan P, Squires JE. Expanding etiology of progressive familial intrahepatic cholestasis. World J Hepatol. 2019;11:450-63. [Crossref]
20. Schukfeh N, Metzelder ML, Petersen C, et al. Normalization of serum bile acids after partial external biliary diversion indicates an excellent long-term outcome in children with progressive familial intrahepatic cholestasis. J Pediatr Surg. 2012;47:501-5. [Crossref]
21. Bull LN, Thompson RJ. Progressive Familial Intrahepatic Cholestasis. Clin Liver Dis. 2018;22:657-69. [Crossref]
22. Maggiore G, Gonzales E, Sciveres M, et al. Relapsing features of bile salt export pump deficiency after liver transplantation in two patients with progressive familial intrahepatic cholestasis type 2. J Hepatol. 2010;53:981-6. [Crossref]
23. Lin HC, Alvarez L, Laroche G, et al. Rituximab as therapy for the recurrence of bile salt export pump deficiency after liver transplantation. Liver Transpl. 2013;19:1403-10. [Crossref]
24. Colombo C, Vajro P, Degiorgio D, et al. Clinical features and genotype-phenotype correlations in children with progressive familial intrahepatic cholestasis type 3 related to ABCB4 mutations. J Pediatr Gastroenterol Nutr. 2011;52:73-83. [Crossref]
25. Vij M, Shanmugam NP, Reddy MS, Sankaranarayanan S, Rela M. Paediatric hepatocellular carcinoma in tight junction protein 2 (TJP2) deficiency. Virchows Arch. 2017;471:679-83. [Crossref]
26. Liu Y, Sun LY, Zhu ZJ, Wei L, Qu W, Zeng ZG. Liver Transplantation for Progressive Familial Intrahepatic Cholestasis. Ann Transplant. 2018;23:666-73. [Crossref]
27. Mehl A, Bohorquez H, Serrano MS, Galliano G, Reichman TW. Liver transplantation and the management of progressive familial intrahepatic cholestasis in children. World J Transplant. 2016;6:278-90. [Crossref]
28. Clayton PT. Disorders of bile acid synthesis. J Inherit Metab Dis. 2011;34:593-604. [Crossref]
29. Teckman JH, Jain A. Advances in alpha-1-antitrypsin deficiency liver disease. Curr Gastroenterol Rep. 2014;16:367. [Crossref]
30. Hidvegi T, Ewing M, Hale P, et al. An autophagy-enhancing drug promotes degradation of mutant alpha1-antitrypsin Z and reduces hepatic fibrosis. Science. 2010;329:229-32. [Crossref]
31. Carey EJ, Iyer VN, Nelson DR, Nguyen JH, Krowka MJ. Outcomes for recipients of liver transplantation for alpha-1-antitrypsin deficiency–related cirrhosis. Liver Transpl. 2013;19:1370-6. [Crossref]
32. Lerut JP, Ciccarelli O, Sempoux C, et al. Glycogenosis storage type I diseases and evolutive adenomatosis: an indication for liver transplantation. Transpl Int. 2003;16:879-84. [Crossref]
33. Chou JY, Jun HS, Mansfield BC. Glycogen storage disease type I and G6Pase-beta deficiency: etiology and therapy. Nat Rev Endocrinol. 2010;6:676-88. [Crossref]
34. Boers SJB, Visser G, Smit PGPA, Fuchs SA. Liver transplantation in glycogen storage disease type I. Orphanet J Rare Dis. 2014;9:47. [Crossref]
35. Karaki C, Kasahara M, Sakamoto S, et al. Glycemic management in living donor liver transplantation for patients with glycogen storage disease type 1b. Pediatr Transplant. 2012;16:465-70. [Crossref]

36. Davies JC, Alton EWFW, Bush A. Cystic fibrosis. BMJ. 2007;335:1255-9. [Crossref]
37. Colombo C, Battezzati PM, Crosignani A, et al. Liver disease in cystic fibrosis: A prospective study on incidence, risk factors, and outcome. Hepatology. 2002;36:1374-82. [Crossref]
38. Molmenti EP, Squires RH, Nagata D, et al. Liver transplantation for cholestasis associated with cystic fibrosis in the pediatric population. Pediatr Transplant. 2003;7:93-7. [Crossref]
39. Melzi ML, Kelly DA, Colombo C, et al. Liver transplant in cystic fibrosis: a poll among European centers. A study from the European Liver Transplant Registry. Transpl Int. 2006;19:726-31. [Crossref]
40. Genyk YS, Quiros JA, Jabbour N, Selby RR, Thomas DW. Liver transplantation in cystic fibrosis. Curr Opin Pulm Med. 2001;7:441-7. [Crossref]
41. Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. Blood. 2012;120:4496-504. [Crossref]
42. Singal AK, Parker C, Bowden C, Thapar M, Liu L, McGuire BM. Liver transplantation in the management of porphyria. Hepatology. 2014;60:1082-9. [Crossref]
43. Wells MM, Golitz LE, Bender BJ. Erythropoietic protoporphyria with hepatic cirrhosis. Arch Dermatol. 1980;116:429-32.
44. Wahlin S, Stal P, Adam R, et al. Liver transplantation for erythropoietic protoporphyria in Europe. Liver Transpl. 2011;17:1021-6. [Crossref]
45. Kim IK, Niemi AK, Krueger C, et al. Liver transplantation for urea cycle disorders in pediatric patients: a single-center experience. Pediatr Transplant. 2013;17:158-67. [Crossref]
46. Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr. 2001;138:S30-9. [Crossref]
47. Yu L, Rayhill SC, Hsu EK, Landis CS. Liver Transplantation for Urea Cycle Disorders: Analysis of the United Network for Organ Sharing Database. Transplant Proc. 2015;47:2413-8. [Crossref]
48. Chapman KA. Practical management of organic acidemia. Translational Sci and Rare Dis. 2019;4:121-31. [Crossref]
49. Blackburn PR, Gass JM, Vairo FP, et al. Maple syrup urine disease: mechanisms and management. Appl Clin Genet. 2017;10:57-66. [Crossref]
50. Strauss KA, Mazariegos GV, Sindhi R, et al. Elective liver transplantation for the treatment of classical maple syrup urine disease. Am J Transplant. 2006;6:557-64. [Crossref]
51. Mazariegos GV, Morton DH, Sindhi R, et al. Liver transplantation for classical maple syrup urine disease: long-term follow-up in 37 patients and comparative United Network for Organ Sharing experience. J Pediatr. 2012;160:116-21. [Crossref]
52. Fuentes-Garcia D, Falcon-Arana L. Perioperative management of a patient with maple syrup urine disease. Br J Anaesth. 2009;102:144-5. [Crossref]
53. Sze YK, Dhawan A, Taylor RM, et al. Pediatric liver transplantation for metabolic liver disease: experience at King's College Hospital. Transplantation. 2009;87:87-93. [Crossref]
54. Mor E, Nesher E, Ben-Ari Z, et al. Sequential liver and kidney transplantation from a single living donor in two young adults with primary hyperoxaluria type 1. Liver Transpl. 2013;19:646-8. [Crossref]
55. Kemper MJ. The role of preemptive liver transplantation in primary hyperoxaluria type 1. Urol Res. 2005;33:376-9. [Crossref]
56. Page MM, Ekinci EI, Jones RM, Angus PW, Gow PJ, O'Brien RC. Liver transplantation for the treatment of homozygous familial hypercholesterolaemia in an era of emerging lipid-lowering therapies. Intern Med J. 2014;44:601-4. [Crossref]
57. Marais AD, Blom DJ. Recent advances in the treatment of homozygous familial hypercholesterolaemia. Curr Opin Lipidol. 2013;24:288-94. [Crossref]
58. Maiorana A, Nobili V, Calandra S, et al. Preemptive liver transplantation in a child with familial hypercholesterolemia. Pediatr Transplant. 2011;15:E25-9. [Crossref]
59. Kawagishi N, Satoh K, Akamatsu Y, et al. Long-term outcome after living donor liver transplantation for two cases of homozygous familial hypercholesterolemia from a heterozygous donor. J Atheroscler Thromb. 2007;14:94-8. [Crossref]
60. Ibrahim M, El-Hamamsy I, Barbir M, Yacoub MH. Translational lessons from a case of combined heart and liver transplantation for familial hypercholesterolemia 20 years post-operatively. J Cardiovasc Transl Res. 2012;5:351-8. [Crossref]
61. Alkofer BJ, Chiche L, Khayat A, et al. Liver transplant combined with heart transplant in severe heterozygous hypercholesterolemia: report of the first case and review of the literature. Transplant Proc. 2005;37:2250-2. [Crossref]
62. Ishigaki Y, Kawagishi N, Hasegawa Y, et al. Liver Transplantation for Homozygous Familial Hypercholesterolemia. J Atheroscler Thromb. 2019;26:121-7. [Crossref]
63. Pfeffer G, Majamaa K, Turnbull DM, Thorburn D, Chinnery PF. Treatment for mitochondrial disorders. Cochrane Database Syst Rev. 2012;2012:CD004426. [Crossref]
64. Avula S, Parikh S, Demarest S, Kurz J, Gropman A. Treatment of mitochondrial disorders. Curr Treat Options Neurol. 2014;16:292. [Crossref]
65. Lee WS, Sokol RJ. Mitochondrial hepatopathies: advances in genetics, therapeutic approaches, and outcomes. J Pediatr. 2013;163:942-8. [Crossref]
66. Cormier-Daire V, Chretien D, Rustin P, et al. Neonatal and delayed-onset liver involvement in disorders of oxidative phosphorylation. J Pediatr. 1997;130:817-22. [Crossref]
67. Frei P, Minder EI, Corti N, et al. Liver Transplantation because of Acute Liver Failure due to Heme Arginate Overdose in a Patient with Acute Intermittent Porphyria. Case Rep Gastroenterol. 2012;6:190-6. [Crossref]
68. Andersson C, Wikberg A, Stegmayr B, Lithner F. Renal symptomatology in patients with acute intermittent porphyria. A population-based study. J Intern Med. 2000;248:319-25. [Crossref]
69. Wahlin S, Harper P, Sardh E, Andersson C, Andersson DE, Ericzon BG. Combined liver and kidney transplantation in acute intermittent porphyria. Transpl Int. 2010;23:e18-21. [Crossref]
70. Levi D, Pefkarou A, Fort JA, DeFaria W, Tzakis AG. Liver transplantation for factor VII deficiency. Transplantation. 2001;72:1836-7. [Crossref]
71. Pescatore SL. Clinical management of protein C deficiency. Expert Opin Pharmacother. 2001;2:431-9. [Crossref]