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Liver transplantation for pediatric inherited metabolic disorders: considerations for indications, complications, perioperative management

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Abstract

Liver transplantation is an effective therapeutic option for a variety of inborn errors of metabolism. This approach can significantly improve the quality of life of patients who suffer from severe disease manifestations and/or life-threatening metabolic decompensations despite medical/dietary management. Due to the significant risks for systemic complications from surgical stressors, careful perioperative management is vital. Even after liver transplantation, some disorders require long-term dietary restriction, medical management, and monitoring of metabolites. Successful liver transplant for these complex disorders can be achieved with disease and patient-specific strategies using a multidisciplinary approach. In this article, we review indications, complications, perioperative management and long-term follow up recommendations for inborn errors of metabolism that are treatable with liver transplantation.

Keywords

Pediatric liver transplantation; inborn errors of metabolism; long-term follow up; perioperative management

Introduction

Recent advances in surgical management and the development of new immunosuppressants have made liver transplantation (LT) a viable therapeutic option for an increasing number of disorders. The main indication for LT in children is biliary atresia after failure of the Kasai

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portoenterostomy. In children with biliary cirrhosis, chronic liver failure and complications of portal hypertension, the purpose of LT is to restore synthetic function by replacing an organ with intrinsically defective architecture. The use of LT for hepatorenal tyrosinemia in 1978 and ornithine transcarbamylase deficiency (OTC) in 1989 represented a new approach to replace a specific functionality - a genetically deficient enzyme activity - in patients with inborn errors of metabolism (IEM) (1, 2).

IEM are a group of disorders that impair the function of a critical pathway in cellular metabolism that may result in severe multisystemic illness or death. There are several types of inborn errors of metabolism that are potentially treatable by LT including inborn errors of amino acid, carbohydrate, metal and lipid metabolism, as well as mitochondrial disorders. The mainstay of treatment for many of these disorders includes specific dietary restrictions to reduce the accumulation of toxic metabolites, supplementation with essential products downstream of the metabolic block and the use of medications to dispose of toxic metabolites or to enhance the residual enzyme activity of the mutant protein. While these approaches are often successful, notably in preventing intellectual disability in phenylketonuria (PKU), medical management can be extremely challenging for patients and their families (3). Barriers to successful medical management include the necessity to adhere to highly restricted diets and special medical formulas, the ongoing risk of life-threatening metabolic decompensation from intercurrent illnesses and, for some families, difficulty in accessing regional centers staffed with IEM specialists.

Following the introduction of LT as a therapeutic modality for IEM, the indications for LT have grown to encompass a broader range of metabolic disorders. According to the SPLIT registry, between 1995 and 2008 a total of 446 patients (14.9% of registered cases) underwent LT for metabolic diseases as a primary indication (4). Among them, urea cycle disorders (UCDs) are the most common indication for transplantation, accounting for 25.6% of the cases (4). This is followed by alpha 1 antitrypsin deficiency (19.7%), cystic fibrosis (10%), Wilson disease (7.6%), maple syrup urine disease (MSUD) (6.5%), tyrosinemia (7.4%), glycogen storage disease (GSD) (5.2%), and other disorders (17.2%) (4). Despite many successful cases of LT, it is well recognized that LT is not a complete cure for some disorders. The anticipated benefit of LT for IEM patients depends on the extent of extra-hepatic manifestations as well as the severity of disease in a given individual. Importantly, even in cases where LT is non-curative, it can provide patients and their families with substantial benefit by reducing the risk of acute metabolic decompensation or stringent dietary restriction, thereby significantly improving their quality of life (5).

The biochemical derangements observed in this patient population are variable and complex and, in some instances, render patients susceptible to metabolic decompensation from intra- and perioperative stress. Therefore, a well-prepared perioperative monitoring and management plan is critical for successful LT for IEM. In this article, we review IEM in which LT may be considered as a therapeutic option and summarize previously suggested monitoring and management plans during and after LT with a focus on disease-specific metabolic management. Other general post-LT managements such as monitoring of surgical complications, usage of immunosuppressants or prevention of infection are not discussed in this article but are available in other reviews (6, 7).

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IEM currently treated with LT and their management

IEM that are candidates for LT can be categorized into two groups depending on the outcome after LT including 1) those that can be cured by LT with no requirement for further management of the underlying IEM and 2) those that can be improved but still need ongoing metabolic management after LT with continuous residual metabolic derangement (Table 1). It is important to note that some genes that have significant extrahepatic expression will still be effectively cured by LT as the residual abnormal metabolites generated by the rest of the body can be efficiently cleared by the donor liver. An example of such a disorder is MSUD, which is caused by mutations in any of several genes encoding a multi-subunit enzyme complex responsible for branched chain amino acid disposal. These genes are highly expressed in liver but are also expressed in muscle (8). Nonetheless, the new graft liver provides sufficient enzyme activity to correct the accumulation of harmful metabolites, eliminating the need for dietary therapy after LT. In the case of disorders with significant extra-hepatic expression and pathology, providing a functional enzyme activity via the donor liver, while not curative, can still have significant beneficial effects on medical management such as liberalized dietary restrictions or reduced requirements for medical therapies.

Considerations for the source of the donor liver include whether to use cadaveric or living related donor LT. The majority of IEM are inherited in an autosomal recessive pattern, in which case parents are obligate carriers. The reduction of enzymatic activity observed in carriers relative to individuals with two functional gene copies suggests that cadaveric livers are more suitable donor organs, particularly for conditions with significant extra-hepatic manifestations. Nonetheless, living related donor LT using obligate carriers has been employed successfully in situations when cadaveric donors were unavailable, particularly in Asian counties such as in Japan, which have a significant shortage of deceased donors (9).

The following section describes disease-specific biochemical derangements and considerations for indications, complications, perioperative management, post-LT management, and expected outcomes.

Tyrosinemia type I

Tyrosinemia type I is an autosomal recessive disorder caused by a deficiency of fumarylacetoacetase (FAH), which is expressed in the liver and kidney (10). Accumulation of maleylacetoacetate and fumarylacetoacetate, and their derivatives, succinylacetone (SA) and succinylacetoacetate, are the pathognomonic biochemical abnormalities. Most patients also have hypertyrosinemia and hypermethioninemia, and elevated serum alpha-fetoprotein (AFP). Clinical manifestations may include liver failure, hypertrophic cardiomyopathy, renal tubulopathy, neuropathy, porphyria-like symptoms, cirrhosis, and hepatocellular carcinoma (HCC). In the past, phenylalanine and tyrosine-restricted diet and LT had been the only treatment options. The outcome of LT has been generally favorable with reversal of liver failure, hypertrophic cardiomyopathy, normalization of plasma tyrosine, AFP and reduction of urine SA level without need for dietary restriction (11). In 1992, 2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione (NTBC) was introduced as a treatment of tyrosinemia type I (12, 13). NTBC is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase and prevents the formation of maleylacetoacetate, leading to decreased production of the

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downstream toxic metabolites. Due to the success of NTBC in combination of dietary restriction of phenylalanine and tyrosine, the indication of LT for tyrosinemia type I has been modified to patients who are resistant to NTBC treatment or who developed fulminant hepatic failure or HCC (11, 13-15). Reflecting this trend, the rate of LT for children with tyrosinemia type I has decreased, while the average age at the time of transplantation increased over the last decade according to a recent review of UNOS (United Network for Organ Sharing) database (4).

While acute metabolic decompensation is rare in patients with tyrosinemia type I, catabolism associated with fasting and surgery may affect liver function and may precipitate porphyria-like crises. Therefore, it is recommended to minimize fasting period before surgery and provide a continuous 10% dextrose infusion.

Post-LT, SA is still detectable in both blood and urine (16, 17). Pierk *et al.* described long-term follow up of nine children with tyrosinemia who all continued to have a persistent excretion of SA up to 14 years after LT (17). As most post-LT patients will be prescribed immunosuppressants that are potentially nephrotoxic and the risk of progressive renal tubular dysfunction post-LT is uncertain, ongoing monitoring of urinary SA excretion and of renal function is suggested. However, the use of NTBC after LT is at this time not uniformly recommended, as the risk of tubulopathy remains unclear.

Wilson disease

Wilson disease is a disorder of copper toxicity caused by a defect in intracellular transmembrane copper transport due to mutations in *ATP7B* gene resulting in abnormal accumulation of copper (18, 19). It may manifest clinically as acute liver failure or chronic liver failure with extra-hepatic organ involvement, including brain, kidney and heart (20, 21). Wilson disease can be medically treated with copper chelation or zinc salts to prevent absorption but LT is required for patients who develop acute liver failure or cirrhosis from chronic liver damage despite medical management (22, 23). LT may be curative and has been reported to reverse neurological dysfunction (23, 24). The outcome of LT for Wilson disease is favorable with a greater than 80% 10-year survival rate in patients with only hepatic manifestations (25, 26). Neuropsychiatric presentation is a strong predictor of worse outcomes with significantly lower survival rates after LT for those with, compared to those without, neuropsychiatric symptoms (25, 26). After LT there is no need for a specific metabolic follow up for these patients and their medical management is similar to that of patients without metabolic disease.

Alpha 1 anti-trypsin deficiency

Alpha-1-antitrypsin (AAT) is a protease inhibitor present in human plasma and protects tissues from proteases such as neutrophil elastase (27). Patients with AAT can develop clinically significant liver and lung disease in adulthood. The mutant Z allele of *AAT1* gene results in the accumulation of misfolded mutant protein within hepatocytes, leading to liver injury, cirrhosis, and hepatocellular carcinoma. Additionally, the lungs of the patients that lack circulating AAT are susceptible to proteolytic attack by neutrophil elastase, resulting in emphysema. In principle, LT should stabilize the extrahepatic manifestations of disease as it

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restores the normal production of AAT. Unfortunately, a recent study by Carey *et al.* showed that pulmonary function still continues to deteriorate even after LT despite decent recovery of hepatic function with normal AAT synthesis (28). Therefore, careful pulmonary follow up should be considered for those with abnormal lung function.

The Porphyrias

The porphyrias are a group of disorders caused by enzymatic deficiencies of the heme biosynthetic pathway primarily occurring in the liver and/or bone marrow. LT has been described as a therapeutic option for acute intermittent porphyria (AIP) and erythropoietic protoporphyria (EPP) (29, 30).

Acute intermittent porphyria (AIP)

LT is indicated for intractable neurovisceral symptoms for AIP and it is proposed to be curative. AIP is caused by deficiency of 5-aminolevulinic acid-dehydratase and is characterized by increased hepatic production of porphyrin precursors, resulting in neurovisceral crises such as severe abdominal pain without skin photosensitivity (31, 32). These acute attacks can lead to life threatening coma or respiratory depression. The mainstay of treatment is avoidance of triggering agents, adequate hydration and glucose intake with intravenous hemin provided during acute attacks (33). LT is indicated for AIP patients with severe life-threatening acute attacks or for patients who have recurrent attacks to prevent permanent neurological damages (29, 34). LT for AIP is essentially curative. The majority of transplanted patients remained free from symptoms and LT appears to prevent the development of hepatocellular carcinoma (34, 35). Interestingly, perioperative hepatic artery thrombosis has been reported in four out of 14 reported cases, supporting the necessity of careful monitoring for this complication (31, 34, 36, 37). Dowman *et al.* have incorporated routine use of antiplatelet medications after LT in AIP patients (34). As renal dysfunction is a long-term complication of AIP (35, 38), successful combined liver-kidney transplantation has also been reported (37). Because of the possible risk for kidney involvement, careful perioperative monitoring of electrolytes and blood pressure is important.

Erythropoietic protoporphyria (EPP)

EPP, the most common erythropoietic porphyria, is caused by reduced activity of ferrochelatase (FECH), the last enzyme of the heme biosynthetic pathway (30). A porphyrin precursor, protoporphyrin, accumulates primarily in bone marrow and is eventually taken up by the liver. The condition is characterized by very painful photosensitivity with skin edema, redness and, rarely, vesicles and bullae. Additionally, some patients develop protoporphyrin-induced liver damage, which may be severe enough to require LT (29). The first case of LT for EPP was described in 1980 (39). Since then, more than 50 cases of LT have been reported for EPP (40, 41). According to a retrospective study in the US, six out of 20 patients who received LT were pediatric patients (40). For EPP, LT is not curative because the continuous production of protoporphyrin leads to a high rate of recurrence of liver damage in the graft liver (41). To completely cure this disorder without recurrence of liver damage, bone marrow transplantation is necessary.

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Unique perioperative complications for EPP include phototoxic tissue burns from ultraviolet light emitted by surgical equipment and postoperative neuropathies (42, 43). Pre-operative reduction of the level of protoporphyrin by using inravenous hemin, plasma exchange, or ursodeoxycholic acid and cholestyramine is suggested for the former (29). The etiology of post-operative neuropathy is unclear but it can lead to respiratory failure, requiring close monitoring and support of respiratory function (43).

Maple syrup urine disease (MSUD)

MSUD is an autosomal recessive aminoacidopathy cause by a deficiency of the branched-chain alpha-keto acid dehydrogenase (BCKDH) complex, which is a component of the catabolic pathway of the branched-chain amino acids (BCAAs) leucine, isoleucine and valine. Accumulation of BCAA and their alpha ketoacids leads to ketoacidosis and disturbance of neurotransmitter homeostasis (44). Classic MSUD typically presents as a neonatal encephalopathy, which can be fatal if not treated early and aggressively. Despite long-term treatment with dietary restriction of BCAAs, most MSUD patients have recurrent life-threatening metabolic decompensations during catabolic stress. Patients with poor biochemical control may have significant neurocognitive impairment. LT is a therapeutic option to treat the classical severe type of MSUD. Although BCKDH activity in liver accounts for only about 9% of whole body BCAA metabolism, LT is sufficient to cure MSUD and eliminate the need for dietary protein restriction (8, 45, 46). After LT, the majority of patients with MSUD are metabolically cured with normal BCAA homeostasis and arrest of neurological damage, although LT is not able to reverse the damage that was already present (45, 46). Immediately after LT, leucine levels drop to normal levels in the majority of cases and BCAA levels remain in the normal range on long-term follow up (46).

Patients with MSUD are at risk for hyperleucinemic metabolic decompensation when they are exposed to stressors such as prolonged fasting or surgical procedures. Minimizing pre-surgical fasting, monitoring leucine, pH and glucose levels should be employed during the perioperative period (47-49). In general, metabolic management should be focused on preoperative control of branched chain amino acids as well as perioperative monitoring of serum glucose, fluid and electrolytes in order to minimize catabolism with resulting hyperleucinemia. The Children's Hospital of Pittsburgh has been using a well-established protocol that includes 1) minimizing fasting period before surgery, 2) continuous dextrose infusion at least 7 mg/kg/min upon hospital arrival, 3) strict monitoring of perioperative sodium and water homeostasis, 4) 24-hour availability of plasma amino acid analysis, 5) in-hospital availability of extemporaneous 10% BCAA-free amino acid solution and individual BCAA solutions (46). Plasma BCAA analysis can be used to monitor metabolic status, and it has been shown that leucine levels can be normalized by 6 hours post LT. Monitoring of other essential amino acids may also be useful to manage nutritional support.

Patients with MSUD in general do not need special metabolic monitoring after LT. An important caveat is in the case of patients who receive living related donor livers. The liver provides only minor fraction of total body BCKAD enzymatic activity. While this is sufficient to prevent metabolic crises, decompensation in the setting of acute illness has been reported (45). Patients with heterozygous donor livers should therefore receive counseling

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about this potential risk and metabolic specialists should be consulted if neurological symptoms suggest hyperleucinemia.

Urea cycle disorders (UCD)

The urea cycle is an essential metabolic pathway that helps the body to dispose of nitrogenous waste derived from protein catabolism through the production of urea. Dysfunction of the urea cycle function can be due to an inherited deficiency in any of the enzymes that mediate the reaction's converting ammonia into urea or in the mitochondrial transporters necessary to shuttle reaction intermediates across the mitochondrial membrane. UCDs result in life-threatening hyperammonemia with lethargy, poor feeding, vomiting, cerebral edema, seizures, coma, or death (50). In patients with severe, early onset UCD who survive the initial decompensation, irreversible brain damage and persistent neurocognitive impairment can occur.

The main focus of chronic UCD management is to maintain positive nitrogen balance in the body while minimizing ammonia production. Chronic management of UCD includes the use of a protein-restricted diet, supplementation of deficient amino acids such as arginine and ammonia scavenger medications including sodium benzoate and sodium or glycerol phenylbutyrate to control plasma ammonia level. Despite this management, however, UCD patients can suffer from life-threatening hyperammonemic crises during periods of catabolic stress.

The liver plays a major role in ammonia detoxification with high activity of urea cycle in hepatocytes. UCD is the most common IEM indication for LT. Consistent with the critical role of liver in ammonia clearance, LT has proven to be successful at curing UCD with a high survival rate and rapid normalization of ammonia levels (51-55). OTC is the most common UCD indication, but LT has also been successfully performed in patients with citrullinemia, carbamoyl phosphate synthetase I deficiency (CPSI), argininosuccinate lyase deficiency, and argininemia (51, 53, 56). Post-LT UCD patients should not have further episodes of hyperammonemia and no longer require dietary protein restriction. In Japan, living related donor LT has been done successfully in multiple cases due to very limited deceased donor availability, including a case using a donor liver heterozygous for X-linked OTC deficiency (9, 57). In this setting, only asymptomatic females who are known carriers of OTC deficiency can be considered as donors after careful enzymatic evaluation and symptomatic females should not be utilized as donors.

Perioperative management of UCD should be focused on nitrogen balance to prevent hyperammonemia as a result of an excessive protein breakdown from surgical stress and fasting-related catabolism. Pre-surgical fasting should be minimized with the provision of a high glucose infusion rate upon initiation of fasting, which may be augmented with additional calories via intravenous fat emulsion. If present, hyperammonemia should be corrected before surgery and maintenance ammonia scavenger medications should be administered as needed (58). Monitoring of ammonia during and after surgery is important to confirm metabolic stabilization with the grafted liver.

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Post-operatively, it is well recognized that OTC and CPS1 patients may continue to have low citrulline levels because extrahepatic biosynthesis of citrulline is still deficient (51, 59, 60). Monitoring of plasma citrulline concentration and appropriate supplementation is recommended.

Glycogen storage diseases (GSD)

The most frequent indications for LT among disorders of carbohydrate metabolism are the GSD. Defects in glycogen mobilization can manifest exclusively in liver, in muscle or in both depending on the expression pattern of the involved genes. Glycogen storage disease (GSD) type Ia (von Gierke's disease), a hepatorenal disease which is caused by defects in the glucose-6-phosphate transporter (G6PT)/glucose-6-phosphatase (G6Pase) complex (61), is the most commonly transplanted disorder of carbohydrate metabolism. Other types of GSDs have been treated by LT (62, 63) but the presence of significant muscular and/or cardiac manifestations, such as in GSD IV (64, 65), may make patients with some of these disorders less attractive candidates.

GSD type I accounts for 25% of cases of GSD and LT has been reported as a therapeutic option in selected patients. GSD type Ia is caused by a deficiency of glucose-6-phosphatase with typical clinical symptoms including profound hypoglycemia, lactic acidosis, hypertriglyceridemia, uric acidemia, hepatomegaly, “doll-like face” and failure to thrive. Hepatic adenoma is one of the most common complications during puberty (66, 67). Patients with GSD type Ib have neutropenia and inflammatory bowel disease in addition to the symptoms seen in patients with type Ia. With strict nutritional management, many GSD Ia patients can maintain adequate control of blood glucose and lactic acid levels. However, LT is an option for patients with poor metabolic control, large or inoperable hepatic adenomas that affect biochemical control (type Ia) or recurrent infection from neutropenia in (type Ib) (68). The outcome of LT for GSD type I was reported to be excellent with improvement of hypoglycemia, liver function, physical growth and neutropenia (68-70). The association between neutropenia /neutrophil dysfunction and inflammatory bowel disease in type Ib has been suggested (71-73). Inflammatory bowel disease can be potentially improved after LT in patients with Type Ib. The long-term risk of tumorigenesis after LT remains to be characterized.

The most serious concern during the perioperative period for GSD type I is lactic acidosis and hypoglycemia (63). Stress-induced lactic acidosis can be life-threatening (74, 75). Of note, severe lactic acidosis leading to multiple organ failure and death can occur in the absence of hypoglycemia with surgical stress (75). Elevated stress hormone secretion induces glucogenolysis with glucose-6-phosphate (G6P) generation, which accumulates because of the underlying metabolic defect. This leads to increased flux through the glycolytic pathway and excessive production of lactic acid. To avoid hypoglycemia and lactic acidosis, it is recommended to minimize the duration of pre-operative fasting time and start dextrose infusion at a rate of 4-9 mg/kg/min depending on age (69, 76). During LT surgery, glucose, lactate and pH should be monitored frequently and dextrose infusion rates adjusted to maintain adequate blood sugar levels particularly during the period of hepatic dissection and the anhepatic phase. Infusion of fluid that includes lactate such as Lactated

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Ringer's solution should be avoided. If lactic acidosis occurs, correction with intravenous sodium bicarbonate infusion is usually necessary.

In addition to GSD type I, LT has also been undertaken for other hepatic form of GSD such as type III or type IV (62, 63, 65, 77-79). The number of cases reported is still limited and no specific guidelines are available. However, the importance of management to avoid hypoglycemia as in GSD type I has been suggested (80-82).

LT can treat hypoglycemia and reduce the risk of lactic acidosis in GSD type I (63). Therefore, dietary management for hypoglycemia prevention is no longer necessary. In contrast, GSD Ib related-neutropenia, neutrophil dysfunction, and inflammatory bowel disease still require monitoring after LT. GSD type I is associated with progressive renal disease (83) and LT, unfortunately, does not eliminate the risk of developing chronic renal failure, necessitating monitoring of kidney function (84).

Crigler–Najjar syndrome

Crigler-Najjar syndrome (CN) is a rare, autosomal recessive disorder of bilirubin metabolism that is caused by deficiency of UDP-glucuronyltransferase encoded by the bilirubin-uridine diphosphate glucuronosyltransferase (*UGT1A1*) gene (85). Type I disease (CN1) is characterized by severe unconjugated hyperbilirubinemia and kernicterus can occur if untreated. Intensive phototherapy from neonatal period is essential to avoid kernicterus but LT can be a therapeutic option for patients when phototherapy becomes ineffective or interferes with their life styles later (86). LT or auxiliary liver transplantations have been performed as preventive procedures to counteract severe CNS-related complications (87, 88). In physiological condition, most of the bilirubin is bound to plasma albumin and excessive albumin-unbound bilirubin is the source of kernicterus. Physiological stressors can increase bilirubin-to-albumin ratio, resulting in increased risk for kernicterus (89, 90). During the perioperative period, prevention of an imbalance of bilirubin-to-albumin ratio and avoidance of drugs that displace bilirubin from albumin need to be considered (90). After LT, bilirubin level is normalized and arrest of neurological damage or recovery can be expected if patients receive LT during neurologically pre-symptomatic period (87).

Primary hyperoxaluria

Primary hyperoxaluria type 1 is an autosomal recessive disorder caused by a deficiency of alanine glyoxylate aminotransferase (AGXT) that is expressed in the liver (91). The primary target of the disease is kidney and patients with this condition has an excessive amount of excretion of urinary oxalate and that causes nephrocalcinosis and end-stage renal failure before adulthood (92). Previously, isolated kidney transplant was performed for this disorder but due to the high recurrence of kidney damage in the graft, combined liver and kidney transplantation has been a conventional therapy for these patients (93-95). If combined liver and kidney transplantat cannot be done, sequential transplantation can also be an option, but performing liver transplant first is preferable as long as the affected kidneys still reserve at least some function (96). Living related donor LT from heterozygous donors is a treatment option with favorable outcome (9, 97). The effect of the recovery of AGTX production by graft liver is favorable and the outcome of grafted kidney survival is improved in patients

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after combined liver and kidney transplantation (94, 95, 98). Even after combined liver and kidney transplant, recurrent renal oxalosis may occur and a multidisciplinary management by pediatric nephrologists and transplant hepatologists is suggested.

Progressive familial intrahepatic cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a group of autosomal recessive disorders characterized by cholestasis that leads to liver failure. Depending on the mutated genes involved in bile acid metabolism, PFIC is classified into three types, *ATP8B1* for type 1, *ABCB11* for type 2, and *ABCB4* for type 3 (99). The encoded proteins are all transporters of the hepatocytes mediating cellular transport of bile acid and phospholipid. While those disorders have their own characteristics, they share similarities that include jaundice, hepatosplenomegaly, liver fibrosis pruritis, growth failure and eventually end-stage liver disease during childhood (100). Medical management is generally not effective and patients with PFIC require surgical intervention such as partial external biliary diversion or ileal bypass procedure (101). While there have been some cases of successful symptomatic relief reported, the majority of patients need LT as a curative treatment (101-103).

Since fibrotic changes of the liver tissue is the main pathology, there is no significant risk for metabolic decompensation upon surgical procedure and the outcome after LT for PFIC is favorable with approximately 70% of fist year survival (103, 104). In addition to normalization of liver function, LT has significant positive effects on increase in growth velocity and improvement of pruritis, leading to increased quality of life (103).

Despite favorable outcome of LT for PFIC, there is a unique post-transplant complication particularly for PFIC2. Generally, LT was thought curative for this condition but recurrence of cholestasis similar to the original disease had occurred in the donor liver. (105, 106) This recurrence is due to the development of autoimmunity against BSEP protein, which is encoded by the *ABCB11* gene (105-108). Therefore, careful monitoring of cholestasis for PFIC2 patients after LT is important. Once cholestasis with normal GGT is observed, investigation of anti-BSEP antibodies is considered (107). There has been no specific management for the recurrence of PFIC2 cholestasis after LT but the usage of a chimeric monoclonal anti-CD20 antibody, rituximab, along with plasmapheresis has been reported effective (106, 109).

Familial hypercholesterolemia

Familial hypercholesterolemia is an inherited lipid disorder characterized by severely elevated low-density lipoprotein (LDL) levels that results in early-onset atherosclerosis typically affecting the aortic root with an increased risk of coronary artery disease (110, 111). Patients with this condition show a typical yellowish skin finding, xanthomata. The majority of patients with this condition have mutations in the *LDLR, APOB,* or *PCSK9* genes. Importantly, patients with homozygous mutations in *LDLR* gene have significantly elevated LDL levels with severe atherosclerotic changes that are refractory to standard lipid lowering medical therapy (111, 112). Failure of medical management to control LDL levels can be an indication for LT and can result in a rapid decrease of LDL levels with subsequent improvement of xanthomas. Due to recent advances in management including the

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development of drugs such as statins and effective plasmapheresis, LT for familial hypercholesterolemia has become less common except for cases with homozygous mutation in *LDLR* gene (112, 113).

The long-term benefits of LT on cardiovascular health are still unclear and most patients continue to receive statins even with significant reduction of LDL after LT (112, 114). In cases of combined heart and liver transplantation for patients who had familial hypercholesterolemia and ischemic heart disease, post-transplantation outcomes were reported excellent but some patients require statin to maintain therapeutic levels of LDL (115, 116).

Organic acidemia

Methylmalonic acidemia (MMA) and propionic acidemia (PA) are the most common organic acidemias indicated for LT (4, 117). Both MMA and PA are caused by deficiencies of enzymes involved in metabolism of valine, isoleucine, methionine, threonine, and odd chain fatty acids (methylmalonyl-CoA mutase for MMA and propionyl-CoA carboxylase for PA)(118, 119). The accumulation of organic acids and deficiencies of downstream metabolites results in multi-systemic disease. Infants with the classical forms of MMA and PA typically present with lethargy, vomiting, metabolic acidosis, hyperammonemia and encephalopathy, which can progress to coma or death. Medical/dietary management involves protein restriction and provision of medical formulas, maintenance of acid-base status, carnitine supplementation and antibiotic treatment to reduce intestinal propiogenic bacteria. Because of continuous systemic production of toxic metabolites, the long-term outcome for these disorders is poor even with aggressive medical management. Most patients with classic organic acidemias have recurrent life-threatening metabolic decompensations during periods of catabolic stress. Patients with propionic acidemia may develop intellectual disability, hypotonia, cardiomyopathy, pancreatitis, and osteopenia. MMA patients may manifest these symptoms and may also develop renal failure.

At present, more than 30 cases of LT for organic acidemias have been reported including some cases of combined liver and kidney transplantation in patients with renal failure (4, 120). Most patients who received LT had improved metabolic control and less frequent decompensation after transplantation, however, most still required dietary protein restriction and ongoing long-term monitoring of toxic metabolites, acid/base balance and kidney function. Improvement of cardiac function with normalization of echocardiogram and EKG findings after LT was reported in two PA cases, both of which had cardiomyopathy prior to LT, potentially broadening the indication of LT for PA (121, 122). Because damage in the brain and kidney is progressive and it is unlikely that LT can reverse this damage, planning of LT early in life is suggested.

Perioperative management for organic acidemias is challenging because of the continuous production of organic acid metabolites which can be exacerbated during the stress of surgery. Frequent monitoring of acid-base balance and avoidance of catabolism with a high glucose infusion rate (4-6 mg/kg/min) with additional calories from intravenous fat emulsion is needed. Electrolyte monitoring is essential in MMA patients with renal impairment. A case of hyperkalemia with cardiac arrhythmia during anesthesia for a minor surgery in

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MMA was reported even though the GFR for this patient was normal (123). During LT, metabolic acidosis and hyperammonemia must be closely monitored, with correction using sodium bicarbonate infusion, ammonia scavengers if severely hyperammonemic, and intravenous fluids. Additionally, many patients will require levocarnitine to maintain normal plasma concentrations of free carnitine.

In some poorly controlled MMA patients, plasma methylmalonic acid concentration can be extremely high before LT, particularly in those with renal dysfunction. Two patients who underwent combined liver kidney transplantation had hemodialysis preoperatively and the transplantations were reported to proceed without complication (124). However, a review of 25 cases of LT for MMA in Japan suggested that preoperative hemodialysis did not decrease the risk of metabolic decompensation and it was not necessary for successful LT (125).

Long-term monitoring of organic acid levels is critical for the management of organic acidemias. Even after LT, the levels of organic acids may continue to be elevated, although a significant reduction from the baseline levels is typically observed (126, 127). After LT, regular assessments of biochemical and nutritional status are required at a metabolic specialty clinic. Treatment with protein restriction, levocarnitine, and sodium citrate may need to be continued depending on the degree of residual metabolite production, and many patients may still require medical formulas. In the event of stress such as intercurrent illnesses or elective surgery, metabolic decompensation may occur and should be treated aggressively. LT may not reverse preexisting cardiomyopathy, but may arrest its progression, suggesting that periodic cardiac evaluation by echocardiography may be appropriate (122). Similarly, LT may not improve but possibly prevent worsening of neurologic symptoms in organic acidemias (122, 128).

Mitochondrial disorders

Abnormal mitochondrial function due to alterations of mitochondrial DNA or nuclear genes can cause a wide variety of symptoms (129). The liver is commonly involved in mitochondrial disease, and is typically present in the severe infantile-onset forms, usually in association with dysfunction of other organ systems such as the brain, heart, and kidney. A “mitochondrial cocktail” including Coenzyme Q10 and other vitamins has been used as a part of medical management of mitochondrial disorders to augment respiratory chain function, but the effect on mitochondrial hepatopathy remains undetermined (130, 131). Nonetheless, isolated mitochondrial hepatopathies are a well-described clinical entity (132). The long-term outcomes of patients with mitochondrial hepatopathies are poor as there is no effective treatment (133). Currently, the indication for liver transplantation for mitochondrial hepatopathy is controversial. LT should only be considered after an extensive investigation to exclude extra-hepatic disease. Patients with mitochondrial hepatopathy and CNS involvement have significantly worse post-LT survival rates than patients without CNS disease (134). In patients selected for transplant, the surgical outcome may be satisfactory, but clinical outcomes in published case series have been relatively poor, with late-onset extra-hepatic manifestations of mitochondrial dysfunction possible even after initial negative screens (132, 135). Lee and Sokol summarized the published cases of LT for mitochondrial hepatopathies in the literature and reported an overall survival rate of 30% (132).

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Due to the great variability in symptoms and severity, there are no straightforward recommendations for the perioperative management of mitochondrial hepatopathies. General principles of perioperative considerations were summarized in a review article by Avula *et al* (131). In general, it is important to avoid hypoglycemia but adding extra glucose should be avoided for some patients, particularly those treated with a ketogenic diet (136). Frequent monitoring of lactate, pH and electrolytes is critical as well as cardiac monitoring (131). Some patients are not able to metabolize lactate well and it is recommended to avoid lactate-based IV fluid (137).

Other issues

Living related LT from heterozygous donors

Living related donor LT becomes an option when deceased donors are unavailable as commonly seen in Japan. For metabolic disorders with autosomal recessive inheritance, the majority of the donors are parents who are obligated carriers of the recipients' disorders. While there is limited information available regarding LT from heterozygous donors, an extensive review of living related donor LT was performed using the Japanese multicenter registry by Kawahara *et al* (9). In this study, more than 95% of the donors were parents who were carriers of the recipients' disorders. Among the metabolic disorders indicated for living related donor LT, Wilson disease was the most common (30%) and UCDs (29%: OTC accounts for 20%), MMA (10%), GSD (7.7%), tyrosinemia (6.7%), propionic academia (4.6%) and primary hyperoxaluria (4.6%) (9). Additionally, there are some reported successful cases for MSUD (138-140). Overall, the outcome after employing heterozygous donors was excellent with better long-term survival rate, particularly with Wilson disease and UCDs, while other conditions appeared to have more complications associated with original condition. The authors speculated that this is due to insufficient rescue of ongoing pathological process even after LT as described above (9). Particular caution of living related donor LT from heterozygous carriers of OTC needs to be considered as also described as above.

Anesthesia-related issues

There are no specific guidelines available for precaution/contraindications in the usage for some anesthetic agents. Using midazolam, fentanyl, and sevoflurane seems relatively safe for anesthesia in UCD (141-143). Possible contraindications are suggested for the usage of propofol and muscle relaxants for anesthesia for patients with organic acidemias (144-148). Of note, propofol is prepared as an aqueous solution with soybean oil, which is rich in high polyunsaturated fats including precursors of propionic acid (149). In the case of mitochondrial disease, most anesthetic agents have been reported to depress mitochondrial function but most have also been successfully employed in various settings (136). Because of a wide variety of symptoms and severity in mitochondrial disorders, selection of medications requires considerable attention for each patient. Drug management for LT anesthesia in mitochondrial disorders is well discussed in a review by Vater *et al.* (150).

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Long-term follow up for other issues

For the disorders cured by LT (MSUD, UCD, GSD I), dietary management is generally not required after correction of the underlying metabolic derangement. For conditions incompletely treated by LT, monitoring of extra-hepatic manifestations is crucial (suggested long-term metabolic management plans are summarized in Table 1). For the majority of patients with IEM who received LT, some degree of neurocognitive and/or psychomotor impairment has been observed. In the case series of transplanted MSUD patients, most showed arrest of neurocognitive deterioration after LT, but not reversal of pre-existing deficits (45). Accordingly, the continuation of physical, occupational, and speech therapies is highly recommended.

Conclusions

LT has become an effective therapeutic modality for patients with IEM. Despite the emergence of new generation drugs to modify disease progression for some disorders for which LT is indicated, LT is still an option to cure and/or ameliorate the disease for some IEM, which were previously recognized to be incurable devastating diseases. As described above, each disorder has its own biochemical characteristics. Assessment of the risk and benefit of LT should be addressed thoroughly before LT and careful disease-specific monitoring and management may be necessary even after LT. Long-term effects of LT for IEM are still limited and extensive post-LT cohort analyses are expected in order to achieve more successful LT in the future. With further understanding of natural history, development of new drugs, and long-term complications may enable us to delineate better indication of LT and to improve post-LT management of IEM.

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Table 1

Metabolic disorders that are treatable with liver transplantation

Disorders that can be cured by LT	**Organs/systems to be monitored after LT**
Tyrosinemia type I	Kidney
Wilson disease	CNS**
Alpha 1 antitripsin deficiency	Lung
Acute intermittent porphyria (AIP)	Kidney
Maple syrup urine disease (MSUD)	CNS**
Urea cycle disorders (UCD) Ornithine transcarbamylase deficiency (OTC) Citrullinemia Carbamoyl phosphate synthetase I deficiency (CPSI) Argininosuccinate lyase deficiency Argininemia	CNS**
Glycogen storage disease (GSD) Type Ia, Ib, III and IV	Kidney, Blood/Bone marrow (type Ib), GI tract (type Ib)
Crigler-Najjar syndrome	CNS**
Primary hyperoxaluria	Kidney
Progressive familial intrahepatic cholestasis (PFIC)	Liver, GI tract
Disorders with continuous significant metabolic derangement after LT*	
Familial hypercholesterolemia	Heart
Erythropoietic protoporphyria (EPP)	Liver
Organic acidemia	CNS**, Kidney, Heart

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Disorders that can be cured by LT	Organs/systems to be monitored after LT
Methylmalonic acidemia (MMA) Propionic acidemia (PA)	
Mitochondrial disorders	CNS**, Kidney, Heart

CNS: central nervous system

*General consideration of the requirement of post LT metabolic management by IEM specialists. Metabolic outcome of each patient varies and specific management plans including monitoring of metabolites and the frequency of follow up are at each IEM provider's discretion.

**For patients who had neurological symptoms before transplant.

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