Living Related Liver Transplantation for Metabolic Liver Diseases in Children

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ABSTRACT

Metabolic liver diseases (MLDs) are a heterogeneous group of inherited conditions for which liver transplantation can provide definitive treatment. The limited availability of deceased donor organs means some who could benefit from transplant do not have this option. Living related liver transplant (LrLT) using relatives as donors has emerged as one solution to this problem. This technique is established worldwide, especially in Asian countries, with shorter waiting times and patient and graft survival rates equivalent to deceased donor liver transplantation. However, living donors are underutilized for MLDs in many western countries, possibly due to the fear of limited efficacy using heterozygous donors. We have reviewed the published literature and shown that the use of heterozygous donors for liver transplantation is safe for the majority of MLDs with excellent metabolic correction. The use of LrLT should be encouraged to complement deceased donor liver transplantation (DDLT) for treatment of MLDs.

Key Words: domino liver transplantation, liver transplantation, living related liver transplantation, metabolic liver disease

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Metabolic liver disorders (MLDs) are a common indication for pediatric liver transplantation (LT), accounting for 17% of all pediatric LT in the United States since 1987 (1). Currently, the median waiting period in the United States for LT varies from 113 to 291 days. Only 60–70% of children receive LT within 2 years of listing and there is an annual ~7% attrition on the waiting list due to death or deterioration (2). Various strategies to address this have been proposed, including the use of living donation. The use of living donor LT (LDLT) is increasing in all forms of pediatric liver disease, but remains underutilized in children with MLDs, accounting for <10% of cases in the United States (1,3). By comparison, in our center, the use of LDLT is increasing and accounted for 19% of LT for MLD over the last decade.

LDLT is used more commonly in those MLDs with structural liver disease than those without (1). This pattern presumably reflects concern that heterozygote donors, typically with 50% of normal enzyme activity, may result in less effective phenotypic correction compared to unrelated donor organs. A large experience from multinational centers demonstrates that living related LT (LrLT) from heterozygous relatives for MLDs is effective and has the additional advantage of elective timing (4). In addition, the use of a genetically related donor reduces the risk of chronic rejection (5). To support increased use of LrLT in this area, we have reviewed the published literature regarding the safety and efficacy of LrLT for MLDs.

CLASSIFICATION OF METABOLIC LIVER DISEASES

Individual MLDs were classified based on the tissue expression of the defect (primary hepatic expression or multisystem expression) and the mode of inheritance (autosomal recessive [AR], autosomal dominant, or X linked) (Table 1). In addition, we reviewed the utility of auxiliary partial orthotopic liver transplantation (APOLT) for MLDs.

AUTOSOMAL RECESSIVE CONDITIONS

- Disorders with primary hepatic expression

WILSON DISEASE

Wilson disease (WD) is a progressive copper overload disorder due to mutations in the *ATP7B* gene encoding a copper transporting P-type ATPase. With effective medical therapy, LT is reserved for those with fulminant liver failure or decompensated chronic liver disease (7). After LT, lifelong normal copper metabolism is restored (6).

Published experience, predominantly from Asian populations, has shown that transplants using heterozygous donors are safe with complete functional correction of the defect (7–15). Heterozygotes for WD gene have abnormal ceruloplasmin levels in almost 25% of subjects, most of whom have normal urinary copper excretion (11). In fact, if a donor's serum ceruloplasmin is low before transplant, it persists in most, if not all, recipients and has no impact on the metabolic effect of transplantation (11). If a heterozygote donor also has increased urinary copper excretion, the situation is less clear. Although this finding has been viewed by some as a relative contraindication to donation, effective results have still been achieved in this situation, albeit with higher urinary copper in the patient post transplant (7,13).

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TABLE 1. Proposed classification of metabolic liver disorders

Disorders with primary hepatic expression	Disorders with multisystemic expression
Autosomal recessive • Wilson disease (WD) • Urea cycle defects (UCD) except OTCD • Maple syrup urine disease (MSUD) • Tyrosinemia type 1 • Crigler-Najjar syndrome (CNS) • Glycogen storage disease (GSD) Ia, IIIb, and VI • Primary hyperoxaluria type 1 • Citrin deficiency X-linked • Ornithine transcarbamylase deficiency (OTCD) Autosomal Dominant • Alpha 1 antitrypsin deficiency (A1ATD)* • Familial hypercholesterolemia (FH)†	Autosomal recessive • Organic acidemias (OAs) • Glycogen storage disease (GSD) Ib, IIIa, IV, and IX (most types) • Mitochondrial hepatopathies • Cystic fibrosis (CF) X-linked • *PHKA2*-related GSD IX

*Codominant inheritance.
†Most common inheritance is codominant pattern involving *LDLR* gene.

Potential heterozygous donors should have serum ceruloplasmin and urinary copper levels measured. An isolated low ceruloplasmin level should not be a contraindication to donation, but liver biopsy and/or genetic analysis for other mutations may be considered in those potential donors with high urinary copper levels to exclude presymptomatic cases as the background community incidence of heterozygosity for WD is not very rare.

UREA CYCLE DEFECTS (EXCEPT ORNITHINE TRANSCARBAMYLASE DEFICIENCY)

Urea cycle disorders (UCD) are characterized by recurrent life-threatening episodes of hyperammonemia (16). Severely affected subjects require complex management with multiple medications and severe dietary protein restriction, and even under optimum circumstances rarely escape neurological damage. LT is thus a lifesaving therapy that functionally abolishes the metabolic defect and transforms quality of life. For non-OTCD (ornithine transcarbamylase deficiency) UCDs (carbamoyl phosphate synthetase 1 deficiency, citrullinemia [type I and type II], and arginosuccinic aciduria), LrLT is associated with excellent outcomes and restores normal dietary tolerance, without reported recurrence of metabolic symptoms (17–24).

MAPLE SYRUP URINE DISEASE

Maple syrup urine disease (MSUD) is an organic acidemia caused by deficiency of branched chain keto-acid dehydrogenase enzyme complex (BCKDH). This leads to neurotoxicity due to accumulation of branched chain amino acids (BCAA). Despite appropriate dietary and medical therapy, a high lifelong risk of metabolic crises and neurological injury persists. BCKDH is a systemic enzyme expressed in skeletal muscle (60%), liver (9–13%), brain and kidney (31–33) (25). Although LT replaces only a small percentage of the total amount of enzyme in the body, it is functionally corrective, permitting a normal diet and almost completely abolishing the risk of metabolic crises. One subject has been reported who developed transient leucinosis at 55 months post DDLT during an episode of severe gastroenteritis and dehydration (25). His BCAA levels normalized with supportive treatment only and there were no neurological sequelae.

Given the low concentration of enzyme in the liver, a heterozygous donor might not supply sufficient BCKDH to correct the defect. In practice, however, LrLT for MSUD has proven to be highly effective (26–33). Isolated cases of transient metabolic decompensation have been reported after LrLT during severe intercurrent illnesses (31). One such case was a 20-month child who developed encephalopathy and seizures during episodes of gastroenteritis at 2, 5, and 10 months after LrLT from an obligate heterozygote (29). Plasma levels of BCAA were markedly elevated and alloisoleucine was detected. He responded to dialysis and temporary BCAA restriction but subsequently resumed a normal diet. He subsequently tolerated a normal diet without further episodes for more than 2 years (personal observation P. McKiernan).

Thus LT, regardless of organ type, does not completely abolish the risk of severe metabolic crises in MSUD. Although the risk is very low, it may be greater if the donor is an obligate carrier of MSUD. Hence, LrLT should be used only in MSUD if there are no alternatives.

Of note, MSUD livers are otherwise normal, and as most BCKDH activity is extrahepatic, MSUD livers are a logical source for domino LTs and this should be considered in each case. Many reports have shown their effective use in non-MSUD recipients with no reported metabolic consequences after prolonged follow-up (34).

TYROSINEMIA TYPE 1

Hereditary tyrosinemia type 1 (HT-1) is caused by deficiency of fumaryl acetoacetate hydrolase. It has a variable presentation ranging from hepatic failure in the first months of life to later onset disease characterized by chronic hepatic dysfunction with a high lifelong risk of hepatocellular carcinoma (HCC). Early treatment with 2-(2-nitro-4-trifluoromethylbenzoil)-1,3-cyclohexanedione (NTBC) has revolutionized management of this disorder, with neonatal therapy abolishing the risk of these complications (35). Thus, LT is now reserved for those in whom the diagnosis was delayed, who have either unresponsive liver failure or suspected HCC, or where NTBC is unavailable (35).

LrLT has been widely in HT-1, with patient and graft survival rates similar to other MLDs and with no reported disease recurrence (36–40). Post LT, there is residual succinylacetone production by the native kidney, but this is independent of donor type and does not appear to be clinically significant (35).

CRIGLER-NAJJAR SYNDROME

Crigler-Najjar type 1 (CN-1) is caused by uridine diphosphate-glucuronosyl transferase deficiency, leading to severe unconjugated hyperbilirubinemia with a lifelong risk of neurological

sequelae, including kernicterus (41). Intensive phototherapy is the mainstay of treatment in CN-1 but is very intrusive and becomes ineffective with time. LT provides a functional cure and should be planned before irreversible neurological changes develop (41). LrLT has been reported in 10 cases and proven to be as effective as cadaveric LT with lifelong freedom from the need for phototherapy (19,42,43).

PRIMARY HYPEROXALURIA TYPE 1

Primary hyperoxaluria type 1 is caused by deficiency of hepatic alanine:glyoxalate aminotransferase resulting in oxalate overproduction with nephrocalcinosis, renal calculi, and ultimately renal impairment. Oxalate is only renally excreted and as renal injury progresses, oxalate accumulates resulting in systemic oxalosis with cardiac, ocular, and bone marrow involvement (44). Isolated LT is preferred before glomerular filtration rate (GFR) decreases below 40–50 mL/minute/1.73 m^2. Combined liver + kidney transplant is indicated if GFR falls before 30–40 mL/minute/1.73 m^2 (44,45). The preference of simultaneous or sequential liver-kidney transplant is based on institutional preference, availability of renal replacement therapies, and evidence of systemic oxalate load. In general, sequential transplantation may be preferred except for cadaveric LT. Heterozygous carriers have been used successfully as liver, kidney, and liver-kidney donors with similar metabolic correction to DDLT (45–54).

GLYCOGEN STORAGE DISEASES (EXCLUDING TYPE IV)

The hepatic glycogen storage diseases (GSDs) are a group of disorders characterized by hepatomegaly and hypoglycemia and include type I (a and b), III (a and b), IV, VI, and IX (79–81). All are AR disorders except *PHKA2*-related GSD IX (X-linked). Glycogen storage disease type I (GSD-I) is caused by deficiency of glucose-6-phosphatase (type 1a) or glucose-6-phosphate transporter (type 1b) (79,80). GSD-Ia is characterized by severe hypoglycemia and hepatomegaly, whereas GSD-Ib has the added complications of neutropenia and inflammatory bowel disease. Type-III GSD is a result of debrancher enzyme deficiency (*AGL* gene) with abnormal glycogen accumulation in the liver alone (IIIb) or combined with skeletal and cardiac muscle involvement (IIIa) (79). Clinical presentation is initially like GSD-I, but slowly progressive liver disease and myopathy are common. GSD type VI and type IX are due to deficiency of glycogen phosphorylase (*PYGL* gene) and phosphorylase kinase (*PhK* gene), respectively, and are milder than the other forms of GSD, but may occasionally cause progressive liver disease.

The usual indications for LT include poor metabolic control despite nutritional therapy, progressive liver disease, hepatic adenoma, or carcinoma (55). The hepatic metabolic derangements are reversed by LT with improved growth and quality of life on unrestricted diets. Many reports have shown that LrLT is safe and efficacious in GSDs, with comparable success to DDLTs (55–61). Extrahepatic complications are not impacted by donor type (55).

DISORDERS WITH MULTISYSTEMIC EXPRESSION

Organic Acidemias

Organic acidemias (OAs) are a group of metabolic disorders characterized by systemic accumulation of toxic intermediary metabolites, including methylmalonic acidemia (MMA) and propionic acidemia (PA). MMA is caused by deficiency of methylmalonyl-CoA mutase (or its cofactor adenosyl-cobalamin), whereas PA is caused by deficiency of propionyl-CoA carboxylase, which converts propionyl-CoA to methylmalonyl-CoA (62). Clinical presentation is typically that of ''intoxication-type'' distress in the newborn period with predominant neurological manifestations that may progress to coma and death. Though primary dietary management has evolved, recurrent metabolic crises, poor growth and impaired neurodevelopment are still the rule.

In spite of the multisystem expression of the disease, LT provides an important partial phenotypic correction, permitting relaxation of dietary restriction, significantly reducing the risk of ketoacidotic crises, and improving quality of life (62). However, the risk of extrahepatic complications including renal failure and metabolic stroke persist after LT, albeit less common. LrLT has been shown to be as safe and effective as DDLT in patients with OAs without any evidence of increased burden from extrahepatic disease (19,63–77).

Cystic Fibrosis

Hepatobiliary disease is present in up to 35% of cases of cystic fibrosis (CF), but <10% develop advanced liver disease with portal hypertension. Indications for LT are determined by the severity of liver disease, but the timing of LT will be affected by the severity of lung disease (78). LT is very successful in CF, but long-term survival is limited by progressive lung disease (1). LrLT has been reported in 1 series of 15 pediatric cases where survival was slightly lower compared to DDLT, but few details were provided (78).

GLYCOGEN STORAGE DISEASE TYPE 4

GSD-IV, due to glycogen brancher enzyme deficiency (*GBE1* gene), is a rare multisystemic disease involving liver, muscle, brain, and heart with variable age of onset and severity. It has the highest risk of end stage liver disease among all GSDs. LT has been effective in treating liver failure in GSD-IV patients, but extrahepatic manifestations may persist (79,80). Fatal *de novo* cardiac failure after LT has been reported, but the overall incidence of this is unclear (81). LrLT has been successful in GSD-IV without an obvious difference in outcome compared to DDLT (4,14,79,80,82).

DISORDERS OF MITOCHONDRIAL METABOLISM

This group of disorders affects energy generation by oxidative phosphorylation, resulting in cellular ATP deficiency and subsequent cellular stress and death. The constituents of this enzymatic system are mostly encoded by nuclear DNA, with some encoded by the mitochondrial DNA (mt-DNA). All reported mitochondrial liver diseases are AR, except for Pearson syndrome, which appears to be sporadic. Multisystem involvement is the rule in these disorders, affecting tissues with the highest energy requirements (brain, muscle, liver, eye) (83).

The role for LT in mitochondrial disorders is complex as extrahepatic symptoms may develop or progress after LT. The presence of extrahepatic involvement is often a contraindication to LT, but evaluation of multisystem involvement is difficult, especially in acute cases. Not all extrahepatic disease is fatal, and each case should be judged on its merits (83,84). Given these caveats, even with limited available experience (12 reported cases), LrLT has been as successful as DDLT in mitochondrial hepatopathies and has the benefit of being more readily available in the setting of acute liver failure (84–87).

AUTOSOMAL (CO)DOMINANT CONDITIONS

Alpha 1 Antitrypsin Disease

Alpha 1 antitrypsin deficiency (A1ATD) is an autosomal codominant disorder caused by mutations in the *SERPINA1* gene. The wild-type M allele is present in 95% and a Z allele, encoding an abnormally folded protein, in 2–3% of Caucasians. Individuals homozygous for the Z allele may develop liver disease due to intrahepatic accumulation of misfolded protein and lung disease due to low hepatic secretion of the protein, which normally protects the lungs from damage by neutrophilic elastases. A1ATD is the commonest metabolic disorder requiring liver transplantation in the Western world (1). Standard indications for LT are based on the severity of the liver disease.

MZ heterozygotes appear to be at higher risk of liver disease than the general population, and hence there have been concerns about their use as LrLT donors. Published cases where this has been done have been reassuring in terms of both donor safety and recipient efficacy, and thus it is certainly not a contraindication to donation (88–90). However, long-term surveillance of both donor and recipient appears sensible in order to understand how the heterozygous state affects long-term outcomes. Some reassurance can be gained from the outcome of DDLT undertaken from donors who were unsuspected MZ heterozygotes. As many as 0.8% of presumed healthy transplanted livers are from unsuspected heterozygotes and, in general, these grafts have shown good long-term outcomes despite histological findings, including A1AT granules (91–93).

Homozygous Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a relatively common autosomal disorder resulting in accelerated cardiovascular mortality in adulthood, which usually responds favorably to lipid lowering treatment. Homozygous FH is a devastating condition resulting in cardiovascular death by the second decade which does not respond to lipid lowering treatment (94). Treatment options include LT, which reduces cholesterol by 80% or regular LDL apheresis. Heterozygous donors have been used in 3 cases, and although cholesterol levels were significantly improved, they remained

TABLE 2. Summary of studies in LrLT for MLDs

Diagnosis	Number of subjects	Age range (months)	Follow-up duration (months)	Disease recurrence after LrLT	Recommendation for LrLT
Alpha-1 antitrypsin deficiency	13*	7 to 192	NA	• Theoretical risk with MZ heterozygote of increased susceptibility to acquired liver diseases	• Not a contraindication but long-term follow-up mandatory
Urea cycle disorders (UCDs)	71	3 to 204	3 to 125	• Risk of fatal hyperammonemia following LrLT using heterozygous carrier OTC donors • No risk with other UCDs	• OTC deficiency: • Donor testing for assessing heterozygous status • Carrier donors avoided, unless no other options available • Others: no contraindication
Wilson disease	160	72 to 204	12 to 167	• No reported disease recurrence	• Heterozygous donors can be safely used for donation • Check ceruloplasmin and urinary copper. • Donors with low ceruloplasmin and high urinary copper should have genetic studies and/or liver biopsy to exclude presymptomatic disease.
Organic acidemias	63	7 to 90	1 to 161	• Risk of crises significantly decreased after LT	• Heterozygous donors safe for LrLT • Only partial correction of defect with LT of any type
Maple syrup urine disease	22	11 to 117	6 to 37	• Rare risk of crises during stressors with either DDLT or LrLT	• Theoretically higher risks of crises with heterozygous donor • To be avoided unless no alternatives
Hereditary tyrosinemia type 1	67	5 to 156	7 to 75	• No reported recurrence	• No contraindications
Crigler-Najjar type 1	13	2 to 156	4 to 34	• No reported recurrence	• No contraindications
Mitochondrial hepatopathy	12	1 to 84	1 to 90	• No reported recurrence of liver disease	• No contraindications • Risk of multisystem disease recurrence same as with diseased donor LT
Glycogen storage diseases	35	13 to 216	1 to 64	• No reported recurrence of liver disease	• No contraindications
Hyperoxaluria type 1	17	8 to 204	2 to 137	• No reported recurrence of liver disease	• No contraindications
Cystic fibrosis	15*	NA	NA	• No reported recurrence of liver disease	• No contraindications

LT = liver transplantation; LrLT = living related liver transplantation; MLDs = metabolic liver diseases; OTC = ornithine transcarbamylase.
*Includes cases with living-unrelated LT also.

elevated requiring continued lipid lowering treatment (95–97). The long-term cardiovascular outlook for these recipients is not yet clear. Given the expanding nontransplant options for FH, the use of a heterozygous donor can be justified only where is no other option.

X-Linked Diseases

Urea Cycle Defect (Ornithine Transcarbamylase Deficiency)

OTCD, the most common form of UCDs, is an X-linked disorder. LDLT using unaffected donors has been extremely successful with excellent long-term outcomes for both recipients and donors (4,14,98–100).

Hemizygous males are usually more severely affected than heterozygous females, who can vary from having early onset disease to being lifelong silent carriers. Assessment of carrier status when considering LDLT should include molecular analysis for OTC mutations. Allopurinol loading tests and measuring hepatic enzyme activity have been used to exclude subclinical disease in females before donation (4,99,100). Asymptomatic female heterozygous donors may be considered in circumstances when no other donors or treatment alternatives are available (101).

Auxiliary Partial Orthotopic Liver Transplantation in Metabolic liver Diseases

In APOLT, a liver graft is implanted orthotopically in a patient with noncirrhotic diseases following a partial hepatectomy of the native liver (19). The remnant native liver provides safety in case of graft dysfunction and preserves the potential option of future gene therapy. This technically challenging technique has been largely confined to specialist centers. An Achilles heel of the technique is that without vascular manipulation, allograft dysfunction may result in diversion of portal blood to the native remnant with resulting metabolic decompensation.

Successful APOLT using LrLT has been reported in children with CN-1, PA, OTCD, citrullinemia, and familial hypercholesterolemia (19,102,103). Initial experience was disappointing with suboptimal outcomes compared to DDLT, including increased biliary complications and poorer graft survival (104). However, with increased experience, current short- and long-term outcomes are equivalent to DDLT. Posttransplant recurrences of metabolic crisis have been reported in UCDs and PA but have likely been related to the APOLT technique itself rather than the use of heterozygous donors (19,104). Thus, in experienced hands, living related APOLT is a valid alternative to OLT in selected noncirrhotic MLDs.

To conclude, the published literature suggests that LrLT has excellent outcomes in most types of MLD and its use should be encouraged in an era of ever-increasing transplant waiting list morbidity and mortality (Table 2). In our center, we us this approach to consider LRLT as one of the options in all children being assessed for LT due to MLD.

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