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Long-term survival after liver transplantation in children with metabolic disorders

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Abstract: *Background:* Liver transplantation for inherited metabolic disorders aims to save the patient's life when the disorder is expected to progress to organ failure, and to cure the underlying metabolic defect. *Methods*: We retrospectively analyzed 146 pediatric liver transplants (28 metabolic; 118 non-metabolic) performed between 1986 and 2000. *Results*: Twenty-eight transplants were performed in 24 children with metabolic disease (8 females; 16 males; age range 3 months to 17 yr). Indications included α–1-antitrypsin deficiency (n=8), two cases each of hyperoxaluria type 1, Wilson's disease, hereditary tyrosinemia type I, citrullinemia, methylmalonic acidemia, and one case each of propionic acidemia, Crigler–Najjar syndrome *type I*, neonatal hemachromatosis, hemophilia B, Niemann–Pick disease type B, and cystic fibrosis. Eighteen transplants were whole organ grafts and 10 were lobar or segmental. Auxiliary liver transplants were performed in two patients and three received combined liver-kidney transplants. There were three deaths from sepsis, two from chronic rejection, and one from fulminant hepatitis. Seven of 10 patients currently of school age are within 1 yr of expected grade and three who had pretransplant developmental delay have remained in special education. Actuarial survival rates at 5 and 10 yr are 78% and 68%, respectively, with mean follow-up in excess of 5 yr. These results compare favorably to 100 pediatric patients transplanted for non-metabolic etiologies (65% and 61%, respectively) (p= NS). *Conclusions*: Pediatric liver transplantation for metabolic disorders results in excellent clinical and biochemical outcome with long survival and excellent quality of life for most recipients.

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Key words: liver transplantation – metabolic disorders – pediatric transplantation – metabolic disease

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Introduction

In most pediatric transplant centers, metabolic liver disease is the second most common indication for liver transplantation after biliary atresia (1–4). Liver transplantation in inherited metabolic disorders has a twofold aim: to save the patient's life when the disorder is expected to progress to hepatic (or other organ) failure and to cure the underlying metabolic defect. Unlike patients with biliary atresia who develop symptoms related to chronic liver disease, many patients with metabolic liver diseases are transplanted to prevent potential complications. The clinical status of these patients at the time of transplant is usually better than for other chronic hepatobiliary diseases, and the survival rate of patients is higher (3, 4). In this report, we compare the outcome of pediatric patients transplanted for metabolic disease to children transplanted for non-metabolic etiologies. Additionally, we assessed outcomes in children

Abbreviations: EBV: Epstein–Barr viral syndrome, CNS: Crigler–Najjar syndrome, B-UGT: bilirubin-UDP-glucuronosyltransferase.

with metabolic disease stratified by the presence or absence of underlying parenchymal liver damage.

Patients and methods

Between 1986 and 2000, 124 pediatric patients at the University of Michigan Health System received 146 liver transplants. Of these, 28 transplants were performed in 24 children with liver-associated metabolic disease (8 females; 16 males; mean age 9±6 yr, range 3 months to 17 yr). Indications included α–1-antitrypsin deficiency (n=8), primary hyperoxaluria type 1 (n=2), Wilson's disease (n=2), hereditary tyrosinemia type I (n=2), citrullinemia (n=2), methylmalonic acidemia (n=2), propionic acidemia (n=1) Crigler–Najjar syndrome type I (n=1), neonatal hemochromatosis (n=1), hemophilia B (n=1), Niemann–Pick disease type B (n=1), and cystic fibrosis (n=1) (Tables 1 and 2). Eighteen transplants were whole organ grafts and 10 were lobar or segmental grafts. Auxiliary liver transplants were performed in two patients (Crigler–Najjar; methylmalonic acidemia) and three received combined liver-kidney transplants (hyperoxaluria [n=2]; methylmalonic acidemia [n=1]). Retransplants were performed in four cases (two each of chronic rejection and hepatic artery thrombosis). Initial immunosuppression was based on cyclosporin A (n=20) or tacrolimus (n=4), in combination with steroids and azathioprine (n=17), mycophenolate mofetil (n=4), basiliximab (Simulect, Novartis, Basel, Switzerland) (n=1) or anti-CD3 monoclonal antibody (Orthoclone-OKT3; Ortho Pharmaceuticals, Raritan, NJ) (n=1).

Analysis of patient survival was performed by Kaplan–Meier life-table analysis. Statistical analyses were performed using StatView version 4.5 (Abacus Concepts Inc., Berkeley, CA). Statistical significance was accepted at $p < 0.05$.

Results

In the group with metabolic disease, actuarial patient survival rates at 5 and 10 yr were 78% and 68%, respectively, with mean follow-up greater than 5 yr. These results compared favorably to 100 pediatric patients transplanted for non-metabolic etiologies (65% and 61%, respectively; p = NS vs. metabolic group) (Fig. 1). A subset analysis of patients with metabolic disease and cirrhosis (Table 1) and those with metabolic disease and normal liver function (Table 2), demonstrated comparable actuarial survival rates at 5 yr (79% and 75%, respectively).

Among the 24 children in the metabolic group, 12 were treated for graft rejections by steroid bolus alone (n=4) or in combination with OKT3 (n=8). Three patients developed Epstein–Barr viral syndrome (EBV) and potential post-transplant lymphoproliferative disease. The etiology of metabolic disease in these patients was tyrosinemia, methylmalonic acidemia and Crigler–Najjar. Only one patient had been treated for rejection with steroid pulses and OKT3 prior to the onset of elevated EBV titers; all were successfully treated with a reduction of immunosuppression and intravenous ganciclovir. There were three deaths from sepsis, two from chronic rejection, and one due to fulminant hepatitis (Tables 1 and 2). Seven of 10 patients currently of school age are within 1 yr of expected grade and three who had pretransplant developmental delay have remained in special education.

Discussion

For the majority of children with metabolic disease, the decision to offer liver transplantation is made easily, since the extent of liver damage usually provides a conventional indication. Additional benefits of liver transplantation

Table 1. Metabolic disorders with structural liver disease

Patient number	Diagnosis	Gender	Age at diagnosis	Age at transplant	Graft type (retransplant graft type)	Follow-up (months)	Death
1	α-1-antitrypsin deficiency	M	neonate	9 yr	Whole liver (Left lobe; Left lobe)	54	Y
2	α-1-antitrypsin deficiency	F	neonate	4 yr	Segments II, III, IV	73	N
3	α-1-antitrypsin deficiency	M	neonate	4 yr	Segments II, III, IV	86	N
4	α-1-antitrypsin deficiency	F	6 yr	13 yr	Whole liver	91	N
5	α-1-antitrypsin deficiency	M	neonate	4 yr	Whole liver	66	N
6	α-1-antitrypsin deficiency	M	12 yr	13 yr	Whole liver	24	Y
7	α-1-antitrypsin deficiency	M	15 yr	17 yr	Whole liver	51	N
8	α-1-antitrypsin deficiency	F	4 months	9 yr	Whole liver	19	N
9	Wilson's Disease	F	17 yr	17 yr	Whole liver	18	N
10	Wilson's Disease	F	neonate	17 yr	Whole liver	24	N
11	Tyrosinemia	F	neonate	13 yr	Whole liver	23	N
12	Tyrosinemia	M	neonate	3 yr	Whole liver	18	N
13	Neonatal hemochromatosis	M	neonate	3 months	Segments II, III, IV (Left lobe)	15	Y
14	Hemophilia B	M	21 months	14 yr	Whole liver	30	Y
15	Niemann–Pick Type B	M	12 yr	12 yr	Whole liver	113	N
16	Cystic fibrosis	M	12 months	4 yr	Whole liver	16	N

Table 2 Patients with metabolic disease without structural liver damage

Patient number	Diagnosis (phenotype)	Gender	Age at diagnosis	Age at transplant	Graft type (re-transplant graft type)	Follow-up (months)	Death
17	Primary hyperoxaluria	M	5 months	1 yr	Whole liver Kidney transplant	66	N
18	Primary hyperoxaluria	M	7 yr	8 yr	Segments II, III, IV Kidney transplant	7	Y
19	Citrullinemia	F	neonatal	11 yr	Segments II, III, IV	60	N
20	Citrullinemia	M	prenatal	11 yr	Whole liver	52	N
21	Methylmalonic acidemia (Methylmalonic CoA mutase deficiency)	M	neonatal	16 yr	Whole liver	13	N
22	Methylmalonic acidemia (mutase 0 deficiency)	F	neonatal	13 yr	Heterotopic whole liver Kidney transplant (Heterotopic whole liver)	47	N
23	Propionic Acidemia	M	neonatal	3 yr	Segments II, III	3	Y
24	Crigler–Najjar Type I	M	7 months	10 months	Auxiliary segments II, III	78	N

depend on the type of genetic defect, whether the enzymatic defect is located exclusively in the liver or diffusely throughout all tissues, and the extent and recoverability of extra-hepatic end-organ damage.

For example, in both α-1-antitrypsin deficiency and Wilson's disease, the liver is the main source of enzymatic activity and transplantation provides complete reversal of the metabolic defect. Additionally, in Wilson's disease, where copper overload leads to a progressive accumulation of copper first in the liver and later in other tissues (especially the central nervous system), liver transplantation ameliorates neurological manifestations in most patients (5). Similarly, liver transplantation provides a metabolic cure in hemophilia A and B by providing the missing coagulation protein. However, due to the risks of operation and immunosuppression, liver transplantation should only be performed if hemophilia is complicated by cirrhosis from transfusion-associated hepatitis (6). In hereditary tyrosinemia type I, liver and other organ damage occur due to a widespread enzymatic defect leading to ineffective tyrosine metabolism. Toxic metabolic by-products accumulate and cause severe liver injury ranging from fulminant hepatitis to cirrhosis and hepatocellular carcinoma (7). The kidney and central nervous system are also affected. Liver transplantation treats the liver failure, precludes the development of hepatocellular carcinoma, prevents the recurrence of neurological crises, and may ameliorate renal impairment (8–10). In neonatal hemochromatosis, patients present with fulminant hepatic failure in infancy that usually progresses to death. Liver transplantation offers the opportunity to replace a metabolically defective organ and avoid otherwise fatal outcomes. However, since the etiology of this disorder may be multifactorial (11), surgical cure may only be partial.

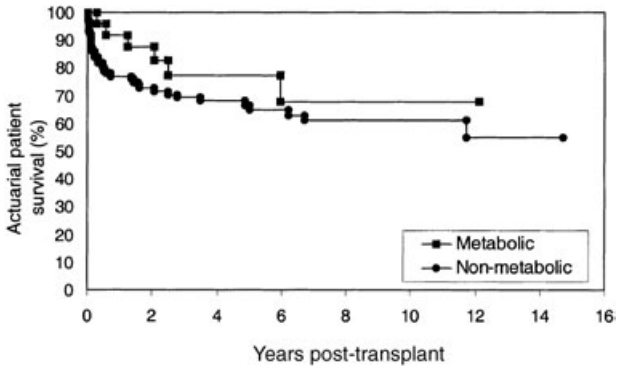

Fig. 1. Actuarial patient survival after liver transplantation.

In a separate group of patients with metabolic disease, the liver remains structurally normal while metabolic disease damages other tissues. The determination as to whether liver transplantation is indicated is more complex, and is dependent on the extent of organ involvement outside the liver and whether liver replacement alone will be sufficient to either prevent further deterioration or improve dysfunction in extra-hepatic organs. Illustrative diseases include primary hyperoxaluria type I, urea cycle disorders, Crigler–Najjar syndrome, and disorders of organic acid metabolism.

Primary hyperoxaluria type I is characterized by the continuous excessive synthesis and excretion of oxalic acid, based on a deficiency of alanine glyoxylate aminotransferase. When the disease is pyridoxine-resistant, oxalosis results in progressive nephrocalcinosis, renal failure, and extrarenal oxalate deposits. The removal of the enzyme-deficient liver and its replacement with a normal one cures the liver-associated genetic defect and prevents the development of renal

disease if performed early enough in the patient's course (3, 12, 13). Unfortunately, many patients develop end-stage renal disease by the time the diagnosis is made. Combined liver and kidney transplantation is necessary in these patients. Isolated kidney transplantation fails to cure the metabolic defect and is usually associated with recurrent oxalate deposition, which often leads to graft failure (14). Auxiliary liver transplantation is not recommended, since the enzymatic defect in the native liver is associated with ongoing excess oxalate production (15).

In urea cycle disorders, the biosynthesis of urea is dependent on six enzymes, all of which are localized in the liver. Patients usually present in infancy with severe and often fatal hyperammonemia (16). Most of those who survive have ongoing cerebral insults with repeated episodes of hyperammonemia, despite intense medical intervention (17). Liver transplantation cures the metabolic defect and prevents irreversible neurologic damage if performed early enough (18, 19). Auxiliary liver transplantation has been advocated by some as a means of preserving the potential for future gene therapy in the native liver and also to preserve the native liver as a reserve in the event of graft failure (18, 19). In our series, two patients were transplanted for citrullinemia. The first child was born with an antenatal diagnosis of citrullinemia by amniocentesis. He initially did well on dietary therapy (protein restriction). However, he subsequently developed frequent episodes of hyperammonemia with progressive behavioral problems and delays in neurological development. Whole organ liver transplant was done at 11 yr of age. At 5 yr follow-up, he has a functioning graft, persistent behavioral problems and is one grade below expected for age. He no longer has hyperammonemia and protein intake has been increased. The second patient presented with hyperammonemic coma after birth. Despite a severely restricted protein diet, she endured many decompensations and suffered from psychomotor retardation. At 11 yr of age she received a cadaveric left lobe transplant, and had an uncomplicated postoperative course. At 5 yr follow-up, she is doing well but remains in special education classes.

Crigler–Najjar syndrome (CNS) is due to a complete (type I) or incomplete (type II) deficiency of the hepatocyte enzyme bilirubin-UDP-glucuronosyltransferase (B-UGT) resulting in unconjugated hyperbilirubinemia (20). CNS type II is distinguished by partial B-UGT activity, which can be induced by phenobarbital to lower bilirubin levels usually at least by 25% (21). Kernicterus is a serious complication of both CNS types I and II (20). It can precipitate without warning and if full-blown is irreversible. Treatment of CNS type I consists of exchange transfusions soon after birth followed by phototherapy until liver transplantation can be done (22, 23). Treatment of CNS type II consists of phenobarbital and the avoidance of drugs that displace bilirubin from its binding to albumin. Children with both types of CNS are usually both physically and mentally entirely healthy, until they suddenly develop kernicterus. For this reason, the decision to transplant an affected child who is jaundiced but otherwise healthy is often postponed, sometimes until it is too late. Auxiliary liver transplantation has been recommended to spare the native liver for possible future gene therapy or hepatocyte transplantation (24, 25). Our patient with Crigler–Najjar syndrome type I received an auxiliary left lateral segment graft at 10 months of age prior to the onset of neurologic deficiencies. He is currently within 1 yr of expected grade at school with good liver function and no hyperbilirubinemia.

Methylmalonic acidemia and propionic acidemia are disorders of organic acid metabolism caused by a defect in methylmalonyl-CoA mutase or its cofactor and propionic carboxylase, respectively. Despite intense medical efforts, accumulation of toxic metabolites usually results in death. The few who survive suffer decompensations and numerous complications, particularly severe cerebral insults (26). Patients with methylmalonic acidemia, in addition, may also develop chronic renal failure (26–28). After liver transplantation, the clinical phenotype is corrected and metabolic decompensations usually do not recur (27, 29). However, since the metabolic error has only been corrected in liver tissue and the liver is not able to clear all extra-hepatic breakdown products of precursor catabolism, patients usually have persistent excretion of urinary metabolites and mild metabolic acidosis. In our series, three patients were transplanted for disorders of branched-chain amino acid metabolism, two with methylmalonic acidemia and one with propionic acidemia. The latter patient did not survive the perioperative period. The two patients with methylmalonic acidemia presented in the newborn period with lethargy, metabolic acidosis and hyperammonemia. Initially, with conventional therapy, they fared well. One patient, who had methylmalonic acidemia due to mutase O deficiency, made appropriate developmental and neurological progress, but because

of early episodes of severe metabolic acidosis, underwent whole liver transplantation at 16 months of age. After 13 months of follow-up he is well with a good quality of life. The other patient had methylmalonic acidemia due to congenital absence of methylmalonic CoA mutase. She developed many late complications of the disease including anemia, pancreatitis, gastrostomy tube dependence, chorea and developmental delay necessitating special education classes. By the age of 8 yr, she was hypertensive with renal failure and had become wheelchair bound. She received a combined heterotopic whole liver and kidney transplant at 13 yr of age. The post-operative course was complicated by hepatic artery thrombosis necessitating another heterotopic whole liver transplant, which was successful. She made a gradual recovery and at 4 yr follow-up, her appetite is improved, she is mildly developmentally delayed and she is ambulatory. This case illustrates the benefit of heterotopic transplantation in the event of graft failure.

Short and long-term survival has been excellent in this current series of patients with metabolic disease, with no operative mortality and 5- and 10-yr survival rates of 78% and 65%. These results are comparable to the 75% to 80% survival rates reported at 5 yr by other centers (2, 30). Currently, all of our school-age survivors are able to attend school. The old paradigm of only transplanting patients with end-stage-liver disease has given way to intriguing circumstances in which transplantation serves to prevent or ameliorate other end-organ damage. Among patients whose metabolic disease threatens the central nervous system, quality of life is particularly improved if transplantation is performed prior to the onset of permanent neurological deficits. Living donors may be especially helpful in this subgroup by providing for timely transplantation. Heterotopic or auxiliary liver transplantation should be considered in some patients with hepatic-based enzyme deficiencies and normal structural liver function to spare the native liver for possible future gene therapy and to provide a hepatic reserve in the event of graft failure.

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