Transplantation for Inherited Metabolic Disorders of the Liver

M.L. Schilsky

ABSTRACT

Inherited metabolic diseases that affect the liver are a frequent cause of liver failure in children, but other disorders more commonly cause liver failure in adulthood where they may present with chronic liver disease and, less frequently, with acute liver failure. The identification of the underlying genetic defect for many of these inherited disorders has improved our understanding of their pathophysiology and impacted on the indications for and timing of liver transplant, yielding better outcomes. Screening for disease and genetic counseling of family members may help prevent adverse outcomes in relatives of affected individuals. Timely liver transplantation offers correction of the inherited metabolic defect and restores liver function when medical therapy is not possible or when complications of liver disease arise. Some inherited metabolic diseases have their defect based in the liver and lead not to liver disease, but to other end organ damage. Earlier detection of these disorders may prevent pathological injury by treatment of the underlying disease or by pre-emptive liver transplant. In some instances where damage of other organs has already occurred, dual organ transplant with liver and another organ may be needed. Improvement in the technical aspects of performing liver transplantation and posttransplant care has led to better outcomes for those with inherited metabolic disorders of the liver.

INHERITED METABOLIC DISORDERS AFFECTING THE LIVER: TRANSPLANT AS "GENE THERAPY"

Inherited metabolic diseases with genetic defects primarily in the liver cells may cause liver injury and liver failure. Although these disorders are a frequent cause of liver failure in children and a leading indication for liver transplantation in the pediatric age group, they represent a minority of transplants in adults. In adults, some inherited metabolic disorders cause liver injury and progressive chronic liver disease leading to liver failure and complications from cirrhosis and portal hypertension, or appear as acute liver failure with characteristics of acute or chronic liver disease. The identification of the underlying genetic defect for these disorders has improved our understanding of their natural history and even permitted pretransplant treatment that has changed the indication and timing of liver transplant, and improved outcomes. Our conceptualization of the natural history and timing for transplant is shown in Fig 1.

When the primary cause for liver disease resides within liver cells, hepatocytes, or cholangiocytes, there is the opportunity for liver transplantation to correct the underlying metabolic defect and provide a "cure" for the disorder. Timely liver transplantation offers correction of the underlying metabolic defect and restores normal liver function. However this cure comes at a cost as there are risks to the recipient related to surgery, risks from donor organ transmission of disease, and risks from side effects of long-term maintenance immune suppression to prevent organ rejection. Examples of when liver transplantation may cure the liver disease include the disorders highlighted in Table 1. For these disorders, the genetic defect has been discovered and the pathophysiology of the disorders mostly known. Several of these disorders are discussed in more detail below where identification of the genetic defect, disease pathophysiology, potential for medical intervention, and indications and outcomes of liver transplant are addressed.

Alpha One Antitrypsin (A1At) Deficiency

A1At is an autosomal recessive disorder of protein processing that causes retention of improperly folded protein in the endoplasmic reticulum of liver cells.[1] Injury to liver cells is thought to occur due to other independent processing

From the Department of Medicine and Surgery, Division of Digestive Diseases, Section of Transplantation and Immunology, Yale University School of Medicine, New Haven, Connecticut.

Address correspondence to M. Schilsky, MD, Yale University Medical Center, 333 Cedar Street LMP 1080, New Haven CT 06520. E-mail: michael.schilsky@yale.edu

360 Park Avenue South, New York, NY 10010-1710

0041-1345/–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.02.001

Table 1. Disorders Where the Defective Gene or Non-functional or Dysfunctional Protein Product Causes Liver Disease

Disease	Gene/Protein	Pathology
Wilson disease	ATP7B	Copper overload liver, nervous system
Hemochromatosis	HFE, hepcidin dysregulation	Iron overload, liver, pancreas, heart Pituitary
Alpha one antitrypsin deficiency	A1At	Protein retention in liver, deficiency in circulation
Tyrosinemia	fumarylacetoacetate hydrolase	Liver failure
Galactosemia	galactose 1-phosphate uridylyltransferase	Liver failure
Neonatal hemochromatosis	Unknown	Liver failure, iron loading
Polycystic disease	Recessive form: Beta-subunit of glucosidase II, Sec63 homologue Dominant form: PKD1, Polycystin	Ductal plate abnormality; cystic disease of the liver and kidneys; hepatic fibrosis
Erythropoietic porphyria	uroporphyrinogen III synthase (bone marrow)	Protoporyphrin biliary secretion and injury, photosensitivity
Cystic Fibrosis	CF gene	Cholestatic liver disease, lung disease

deficiencies for clearance of defective protein, and inter-individual differences in this cellular machinery are thought to be responsible for the differential susceptibility to chronic liver disease.[2] With liver retention of defective A1AT, the low level of anti-protease activity provided by this normally secreted protein leads to the injury of other tissues, in particular the alveoli of lungs with resultant emphysema.[3] The misfolded A1At protein in A1AT disease is most commonly associated with the homozygous genotype ZZ, so named for the migration of the abnormally folded protein on electrophoresis (normally folded wild-type protein is MM). A1At can present acutely in childhood but in some instances resolves spontaneously. In adults, it is usually detected in some with emphysema or found in patients with cirrhosis of previously uncertain origin. Higher rates of liver cancer are found in A1At due to hepatic inflammation and increased liver cell turnover.[4] Liver transplant eliminates liver injury and restores circulating levels of A1At thereby preventing progression of lung damage. The timing of liver transplant for A1At is determined by the presentation. For acute liver failure, emergent liver transplant is needed. For advanced liver disease, early transplant is better to prevent deterioration in pulmonary function and eliminate the risk of malignant transformation of hepatocytes. Outcomes for graft and patient survival for pediatric liver transplant for A1At as reported by a single major center have improved significantly to 100% one year with the change to tacrolimus based immune suppression and overall better management of transplant recipients.[5] Large series of adult with A1At and their outcomes with liver transplant are not available, but it is generally believed that timely transplant can help prevent progression of the pulmonary manifestations of A1At deficiency.

Wilson Disease

Wilson disease (WD) is caused by a defect in the gene *ATP7B* that encodes a copper transport protein expressed mainly in hepatocytes.[6] This disorder presents as acute liver failure in a minority (about 5%) most commonly in the second decade of life, or as end stage liver disease in the third and fourth decades. WD is the result of pathologic copper accumulation in the liver and then in other organs (most commonly the brain). Medical therapy is life-long and consists of treatment with copper chelation to remove copper or zinc salts to prevent copper absorption. The neurological system is an important site for copper induced injury, but symptomatic disease may be prevented by pre-emptive medical treatment or by liver transplantation for those with appropriate indications. Transplantation is "curative" in restoring normal biliary copper excretion and helps promote removal of copper from extra-hepatic sites where it may be toxic.[7] Indications for liver transplant for Wilson disease are acute liver failure or end stage liver disease too far advanced to respond to medical therapy. A scoring system to help prognosticate whether a WD patient would respond to medical therapy was developed by examining outcomes in a pediatric cohort where medical therapy was the only option.[8] In this study, patients with scores greater than 10 (components of the score being WBC, albumin, INR and bilirubin) did not survive with medical therapy. By extrapolation, we can conclude that WD patients with advanced liver disease with scores >10 will die without transplant. Transplantation primarily for neurological WD is controversial due to the ability to treat most of these patients medically, but there are reports of some neurological symptoms improving after transplant as well as permanent disability if transplant is performed after severe injury.[9,10]

Understanding the pathophysiology has impacted practice for WD patients with acute liver failure. These patients require transplant as outcomes with medical therapy alone are extremely poor. While awaiting liver transplant, acute removal of the large excess of copper from the circulation by any of several methods is useful for patient stabilization. These methods include MARS, albumin dialysis, phasmapheresis or exchange transfusion to reduce hemolysis and slow renal injury and help stabilize the patient.[6] Long-term outcomes for adult and pediatric patients with Wilson disease posttransplant are excellent as demonstrated in single case series and in a recent review of data from the US transplant demonstrated in single case series and in a recent review of data from the US transplant