

Donors for Recipients with Hereditary Liver Disease

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ISSUE

Is the donor evaluation modified for recipients with hereditary disease?

BACKGROUND

Between 47%-67% of living donor liver transplants from 2015-2019 were between biological relatives.(1). There is no guidance for modification of the donor evaluation based on a biologic relationship. Here we review the common hereditary liver disorders and the significance of identifying asymptomatic carriers.

DATA

Many inherited liver diseases become apparent early in life and hence transplant outcome data are most robust in the pediatric population. The majority of inborn errors of metabolism and bile acid synthesis defects are autosomal recessive and are associated with a metabolic enzyme deficiency. The heterozygote state of an autosomal recessive condition is generally benign with the use living donors with the heterozygous state demonstrating no negative impact on donors or recipients.(2-4) Alternately, autosomal dominant, X-linked or autosomal recessive disorders with variable penetrance may warrant additional consideration:

Alagille Syndrome is an autosomal dominant disorder (JAG1 or NOTCH2) characterized by paucity of intralobular bile ducts, dysmorphic facies, and other systemic manifestations. Affected first degree relatives may not always be apparent phenotypically based on physical characteristics. In case series evaluating 38 related potential live donors of Alagille recipients, 4 were excluded based on paucity of bile ducts by imaging or biopsy, one underwent donation with unrecognized bile duct paucity with resulting graft dysfunction in the recipient and 2 operations were aborted when aberrant biliary anatomy became apparent during the donor operation.(5, 6) Hence, the affected parent can be ruled out as a living donor with genetic testing if the genotype of

the affected child is known. When genotype is not known, high quality imaging of the donor with or without liver biopsy can be considered to evaluate for biliary paucity.

Ornithine transcarbamylase (OTC) deficiency has an X-linked inheritance pattern while the other urea cycle disorders are all autosomal recessive. OTC deficient homozygous males are usually more severely affected than heterozygous females. The use of asymptomatic heterozygous female donors has only been reported in Japanese live donor literature with complications of hyperammonemia after transplantation.(7) Therefore, assessment of OTC activity in first degree relatives can allow for selection of non-affected relatives as living donors.

Progressive familial intrahepatic cholestasis (PFIC) is a class of genetic disorders altering bile transport. PFIC 1 (ATP8B1) and PFIC 2 (ABCB11) are acquired early in infancy or childhood. PFIC 2 is a rapidly progressing subtype. PFIC 3 (ABCB4) can present at any age. A study looking at the heterozygote state of the ABCB4 mutation demonstrated that cholestatic disease and cirrhosis can develop in adults.(8) Hence, genetic testing for first degree relatives with PFIC3 may be considered if the genotype is known.

Wilson's Disease is a disease of impaired copper metabolism (ATP7B), inherited in an autosomal recessive fashion. While transplantation using a heterozygote donor has been considered safe (3, 9), it should be noted that affected homozygotes may be asymptomatic until later in life. Identification of affected first degree relatives is possible by identifying the genetic mutation of the affected recipient.

Hereditary Hemochromatosis is an autosomal recessive disorder of iron metabolism and remains one of the most commonly identified genetic disorders of Caucasians. Homozygous mutations in the HFE gene (C282Y) account for the majority of affected patients, though compound heterozygotes can rarely be affected (C282Y/H63D or C282Y/S65C). Non-HFE genetic mutations in regulatory proteins such as hepcidin have been implicated as well. Transmission of hereditary hemochromatosis through transplantation has been documented.(10, 11) Iron studies, liver biopsy, or genetic testing of available genotypes will identify at-risk donors.

Alpha-1 antitrypsin (A1AT) deficiency is an inherited liver and lung disease (SERPINA1). There are over 100 variants leading to a wide spectrum of disease severity. The normal gene product is PiM, and the most common mutations are PiS and PiZ, which express 50–60% and 10–20% of the normal A1AT protein and lead to liver and lung disease.(12) A donor with PiZZ, PiSZ, or PiSS is at risk of hepatic and pulmonary manifestations. A small retrospective review of 11 A1AT heterozygote donors (PiMZ, PiMS, and other more rare phenotypes) provides acceptable outcomes.(13) Taking a personal or family history of lung or liver dysfunction should provide useful information when evaluating the living donor and considering the presence of alpha-1 antitrypsin deficiency. Phenotype as well as genotype testing may be useful in identifying living donors who are carriers or not symptomatic. Again, liver biopsy may be useful by identifying periodic acid-Schiff stain (PAS) positive globules to make the diagnosis.

	Inheritance Pattern	Affected Gene	Serologic Screening or Clinical Manifestation	Recommendation
Alagille Syndrome	Autosomal Dominant	JAG1 or NOTCH2	Paucity of intralobular bile ducts, dysmorphic facies	Test all 1 st degree relatives for known genotype
Ornithine transcarbamylase (OTC) deficiency	X-linked	OTC	Arterial pH, carbon dioxide, serum ammonia, lactate, glucose, electrolytes, and amino acids, and urine organic acids and orotic acid	Screen mother (heterozygous female)
Progressive familial intrahepatic cholestasis (PFIC)	Autosomal Recessive	ATP8B1 (PFIC 1), ABCB11 (PFIC 2), ABCB4 (PFIC 3)	Liver enzymes, serum bile acids	For PFIC 3, test all donors for known genotype
Wilson's Disease	Autosomal Recessive	ATP7B	Ceruloplasmin, 24 hour urine copper	Screen all donors for abnormal copper metabolism
Hereditary Hemochromatosis	Autosomal Recessive	HFE	Transferrin saturation, ferritin	Screen all donors for abnormal iron metabolism
Alpha-1 Antitrypsin Deficiency (A1AT)	Autosomal Codominant	SERPINA1	A1AT phenotype, protein levels	Test all donors for A1AT phenotype. If ZZ, SZ, or SS: not a donor candidate; if MZ or MS: may warrant consideration

RECOMMENDATIONS

1. Donors who are biologically related to potential recipients with hereditary liver disease should be screened for that same disease process. When available, knowledge of the genetic mutation in the recipient allows for targeted testing of the donor.
2. Minimizing risk in living donor liver transplantation requires consideration of hereditary liver disease in biologically related donor - recipient pairs. Identifying these disorders is beneficial to the long-term outcomes of the donor and recipient.

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