Liver Transplantation in Alpha-1 Antitrypsin Deficiency

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KEYWORDS

• Alpha-1 antitrypsin • Liver transplantation • Chronic obstructive pulmonary disease

KEY POINTS

- Liver transplantation for Alpha-1 antitrypsin deficiency accounts for a small portion of total liver transplants in the United States.
- The recipient assumes the phenotype of the donor; thus, liver transplantation is considered a cure for the underlying metabolic deficiency.
- Long-term outcomes and preservation of lung function after transplant are not well studied.
- Increased risk of hepatocellular carcinoma requiring liver transplantation is controversial.

INTRODUCTION

Alpha-1 antitrypsin (AAT) deficiency is a genetic condition that increases the risk for liver disease and chronic obstructive pulmonary disease (COPD). The protein deficiency was first described in 1963, and it was recognized that 3 of 5 patients had emphysema at a young age.[1] Several years later, the connection to liver cirrhosis in children was recognized.[2] Research over the last 50 years has led to a better understanding of the pathophysiology and the clinical consequences of both lung and liver disease.[3] However, highly effective therapies remain elusive. Liver transplantation (LT) is considered a "cure" for the condition because the donor liver is able to produce adequate serum levels of AAT. However, transplant is not a practical treatment for everyone affected with AAT, and consideration of LT is limited to those with complications of cirrhosis.

EPIDEMIOLOGY AND GENETICS

AAT deficiency is defined as the inheritance of 2 severe deficiency alleles in the *SERPINA1* gene (**Table 1**). It is an autosomal-recessive disorder with codominant

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Table 1
Phenotype, genotype, and disease risk in alpha-1 antitrypsin deficiency

Inherited Alleles	Phenotype	Serum Protein Levels[a]	Risk of Liver Disease
MM	M	Normal (100%)	None
ZZ	Z	Very low (<15%)	High
MZ	MZ	Intermediate (60%)	Possibly increased
SZ	SZ	Low (35%)	Possibly increased
MS	MS	Intermediate (80%)	None

[a] Serum protein levels are approximations of what is expected in an MM; heterozygotes can have levels that overlap with normal ranges.

expression, with each allele contributing equally to the total circulating level of protein. More than 100 genetic variants of AAT have been described, but most are not associated with liver disease. The most common allele for the AAT gene is designated "M," and the predominant phenotype in the US population is PI*MM. Under these conditions, AAT is present in normal serum concentrations of 120 to 200 mg/dL. The deficiency allele classically associated with clinical disease states is designated as "Z." Individuals who are homozygous (PI*ZZ) have the lowest serum concentration of AAT, usually less than 50 mg/dL, and are at risk for both liver and lung disease. Population screening studies estimate the prevalence for PI*ZZ to range from 1 in 2000 to 1 in 5000.[4–6] The risk of liver disease in carriers (PI*MZ) has also been reported because they are typically overrepresented among individuals with chronic liver disease.[7] The S variant is another common deficiency allele, but it is not associated with liver disease unless a Z is also present. Rare alleles, M_{Malton} and M_{Duarte}, deserve mention because they are also associated with liver disease.[8] Null variants are also rare, but they are highly informative about mechanisms of disease because no liver disease occurs in this phenotype. Null mutations generally occur due to the presence of a premature stop codon, which results in essentially zero production of AAT. No abnormal AAT protein accumulates in the liver.[9]

PATHOGENESIS

The signature feature of AAT deficiency on a liver biopsy specimen is the presence of periodic acid-Schiff-positive (PAS^+), diastase-resistant globules. The globules represent the polymerization of the abnormally folded Z protein retained within the hepatocyte. It is the retention of the AAT within the endoplasmic reticulum of the hepatocyte that is the inciting event in the pathogenesis of liver disease. Normal cellular mechanisms such as endoplasmic reticulum–associated degradation and macroautophagy dispose of the AAT, but when the capacity of these processes is overwhelmed, AAT polymerization and accumulation occur. It is hypothesized that the cells with differing burdens of AAT accumulation (high vs low) may have different fates, but ultimately, cell death, liver fibrosis, and cirrhosis can occur.[10] Detailed discussion is beyond the scope of this review, but several excellent reviews of the pathogenesis have been recently published.[11,12]

ALPHA-1 ANTITRYPSIN DEFICIENCY AND LIVER DISEASE IN CHILDREN

Most AAT-deficient infants are clinically healthy and remain so throughout childhood. Evidence for this comes from a Swedish neonatal screening study of 200,000 infants, which detected 127 PI*ZZ individuals and followed them prospectively into