Alpha-1-antitrypsin Deficiency

Definition

Alpha-1-antitrypsin (AT) deficiency is the most common genetic cause of liver disease in childhood and is the most frequent genetic diagnosis for which liver transplantation is carried out. Alpha-1-antitrypsin deficiency also causes chronic hepatitis and hepatocellular carcinoma in adults. The classical form of the deficiency is caused by homozygosity for the Z allele of AT. Liver injury and carcinogenesis has also been observed in compound heterozygotes for the S and Z alleles, the so-called SZ phenotype. There are over 100 other alleles at the human AT locus. A few others have been associated with liver disease but these alleles are exceedingly rare and so they are not considered in the usual differential diagnosis of liver disease.

Diagnosis of AT deficiency is defined as low serum levels of AT associated with a PI phenotype of ZZ or SZ, or genetic testing indicative of ZZ homozygosity or SZ compound heterozygosity.

Normal Physiology of AT

AT is a 55 kilodalton secretory glycoprotein predominantly derived from the liver. It circulates at a concentration of 150-300 mg/dl, second only to albumin as the most abundant secretory product of the liver. It is also synthesized in extrahepatic cell types including blood monocytes, tissue macrophages and a number of epithelial cell types including intestine and respiratory epithelia. It is an acute phase reactant with plasma concentrations rising 3- to 5-fold during the host response to tissue injury and inflammation.

Although it was first identified as an inhibitor of trypsin in vitro, the rate with which it inhibits neutrophil proteases, such as elastase, cathepsin G and proteinase 3, is higher by several orders of magnitude and inhibition of these proteases is now believed to be its true physiologic function in vivo. AT is the archetype of a family of structurally related proteins called "serpins", many of which are serine protease inhibitors or carrier proteins that bind proteases or ligands by a unique and highly conserved mechanism. Indeed, in a manner almost identical to other serpins, AT allows its target proteases to bind directly to a substrate-like region within its reactive center loop. This interaction leads to structural rearrangement of AT, hydrolysis of its reactive site peptide bond and crushing/inactivation of the target protease. Hydrolysis of the reactive site bond of AT is inactivating and so AT and the serpins are referred to as 'suicide inhibitors.' The reactive site amino acid of AT is methionine. Oxidation of that methionine, as might occur when active oxygen
intermediates are released by bronchoalveolar macrophages during cigarette smoking, leads to functional inactivation of AT as an elastase inhibitor.

**Etiology and Genetics**
A single nucleotide substitution results in a single amino acid change, glutamate 342 to lysine for the Z variant, glutamate 264 to valine for the S variant. The mutant protein is retained in the endoplasmic reticulum of liver cells rather than secreted into the blood and body fluids. ATZ and ATZ variants also polymerize. An 85-90% reduction in serum levels of AT results for ZZ homozygotes and a 60-70% reduction for SZ compound heterozygotes.

The deficiency state is inherited as an autosomal co-dominant. Although there are some studies that suggest that liver injury occurs in the Z heterozygotes, these studies are retrospective and biased in ascertainment. So, even though there is a clear impression that heterozygosity for the Z allele predisposes to liver disease to some extent, the existing data are not sufficient to permit a definitive conclusion.

**Epidemiology**
The incidence of the ZZ homozygous state is 1 in 1800 to 1 in 2000 live births in most populations that have been studied. A nationwide prospective screening study carried out in Sweden in the early 1970s identified over 180 infants with the ZZ or SZ genotype. These infants have been followed over 30 years and the results show that only 8-10% of ZZ homozygotes and SZ compound heterozygotes develop clinically significant liver disease within the first 3 decades of life. Autopsy studies have shown that the ZZ homozygous state is associated with a statistically significant increase in the incidence of cirrhosis and hepatocellular carcinoma. It is not known what proportion of the 90-92% of patients identified in the Swedish nationwide study that have not developed clinical liver disease during the first 3 decades will have liver disease and/or hepatocellular carcinoma that becomes clinically evident later in life or is found incidentally at autopsy. The prevalence of emphysema is not known.

**Pathogenesis of Liver Disease**
Liver disease is caused by a gain-of-toxic function mechanism. This was best demonstrated by experiments in mice transgenic for the human ATZ gene. In transgenic mouse models derived in several different laboratories, there are PAS-positive, diastase resistant globules in hepatocytes and the development of liver injury early in life.
A substantial number of these lines go on to develop hepatocellular carcinoma later in life. Because there are normal levels of AT and presumably other anti-elastases in these animals, as directed by endogenous murine genes, the liver injury/carcinogenesis cannot be attributed to proteolytic attack. According to the gain-of-toxic function paradigm, retention of the mutant protein within the endoplasmic reticulum of liver cells initiates a series of events that are toxic and promote carcinogenesis. The exact mechanism of liver cell injury is not known but there is evidence for mitochondrial dysfunction, activation of mitochondrial and ER caspases and activation of NF?B. This could mean that active oxygen intermediates released by injured mitochondria and inflammatory infiltration mediated by NF?B targets, like interleukin-8, contribute to liver cell injury.

The mechanism of hepatocarcinogenesis is also not known but recent studies have suggested that cells damaged by accumulation of ATZ survive inappropriately and release signals leading to hyperproliferation of cells with lesser accumulation of ATZ that have a selective proliferative advantage. Chronic regeneration in the presence of tissue injury results in adenomas and ultimately carcinomas.

Recent studies have suggested that the tendency of mutant ATZ to polymerize plays a specific role in the mechanism of liver cell injury and carcinogenesis in that nonpolymerogenic AT mutants that are retained in the ER activate different signal transduction pathways than ATZ. For instance, the nonpolymerogenic AT mutants activate the unfolded protein response which would likely result in cell death. Mutant ATZ does not activate the unfolded protein response and hepatocytes which have accumulated enough ATZ to form intracellular globules are characterized by a relative failure to undergo cell death.

Although the condition does not affect children and rarely manifests clinically before the end of the third decade of life, many AT-deficient individuals develop destructive lung disease/emphysema. Lung injury in AT deficiency results from a loss-of-function mechanism whereby decreased number of AT molecules within the lower respiratory tract allow unregulated proteolytic attack on the connective tissue matrix of the lung. Cigarette smoking markedly accelerates the lung injury as a result of oxidative inactivation of residual ATZ by phagocyte-derived active oxygen intermediates. Moreover, the elastase-antielastase theory for the pathogenesis of pulmonary emphysema is based on the concept that oxidative inactivation of AT as a result of cigarette smoking leads to an imbalance favoring elastase activity ultimately leading to the breakdown of the connective tissue matrix of AT-sufficient individuals, the vast majority of patients with emphysema.
Clinical Manifestations of the Liver Disease

Liver involvement is most commonly noticed first at 1-2 months of age because of persistent jaundice. Conjugated bilirubin levels in the blood and serum aminotransferase levels are mildly to moderately elevated. Blood levels of alkaline phosphatase and γ-glutamyl transpeptidase also may be elevated. The liver may be enlarged. There is a tendency for some of the affected infants to have been small for gestational age. Because these clinical and laboratory characteristics are similar to other causes of liver injury in the newborn period, these infants may initially be given the diagnosis of "neonatal hepatitis syndrome" and subjected to a diagnostic evaluation for many different disorders including AT deficiency. Infants also may be evaluated initially for AT deficiency because of an episode of gastrointestinal bleeding, bleeding from the umbilical stump or bruising. A small number of affected children, ~10% of the deficient population, have hepatosplenomegaly, ascites and liver synthetic dysfunction in early infancy and childhood. A few infants are recognized initially because of a cholestatic clinical syndrome characterized by pruritus and hypercholesterolemia. The clinical picture in these patients resembles extrahepatic biliary atresia, but histologic examination of the liver shows paucity of intrahepatic bile ducts and the presence of PAS-positive, diastase resistant globules in the peri-portal hepatocytes.

Liver disease associated with AT deficiency may also be discovered first in late childhood or early adolescence when the affected individual develops abdominal distension from hepatosplenomegaly or ascites, or upper or lower gastrointestinal bleeding from esophageal varices. In some of these patients there is a history of unexplained prolonged obstructive jaundice during the neonatal period. In others, there is no evidence of any previous liver injury, even if the neonatal history is reviewed carefully.

AT deficiency should be considered in the differential diagnosis of any adult who presents with chronic hepatitis, cirrhosis, portal hypertension, or hepatocellular carcinoma of unknown origin. An autopsy study in Sweden shows a higher risk of cirrhosis in adults with AT deficiency than was previously suspected and shows that AT deficiency has a strong association with primary liver cancer. Moreover the risk of liver cancer is greater than can be accounted for by the known increase associated with cirrhosis alone. Interestingly, cirrhosis and liver cancer may be initially diagnosed in a patient with very little in the way of clinical manifestations of liver disease, perhaps just asymptomatic hepatomegaly, elevated transaminase or bilirubin levels. Primary liver cancer is also observed in the absence of cirrhosis in some patients with AT deficiency. The histology of hepatic cancer can be characteristic of hepatocellular carcinoma, cholangiocarcinoma or have features of both.
Although it is not easy to characterize the natural history of the disease in a stereotypical fashion, there are four general scenarios that predominate. The most common scenario is an infant with prolonged obstructive jaundice, mildly elevated serum transaminase levels but no clinical signs of liver dysfunction that goes on to a completely asymptomatic childhood and adolescence. In this group there may or may not be mildly elevated transaminase levels in a persistent or intermittent pattern. It is not yet known whether some of these individuals have subclinical hepatic disease that manifests later in adulthood with severe liver disease and/or hepatocellular carcinoma. A second scenario is very similar to this except that the affected infant develops clinically significant liver disease later in childhood or adolescence. A third scenario is the infant with prolonged obstructive jaundice that goes on to a course of slowly progressive liver dysfunction without any honeymoon period. A fourth scenario is the new onset of portal hypertension during late childhood, adolescence or during adult life without any history of neonatal jaundice or liver injury of any kind.

**Diagnosis**

Diagnosis is established by a serum AT phenotype determination in isoelectric focusing or by agarose electrophoresis at acidic pH. The phenotype should be determined in cases of neonatal hepatitis or unexplained chronic liver disease in older children, adolescents and adults. It is particularly important in the newborn period because it may be very difficult to distinguish patients with AT deficiency from those with biliary atresia. Moreover, it is not uncommon for neonates that are homozygous for ATZ to have no biliary excretion on scintigraphic studies.

Serum concentrations of AT can be used to screen for AT deficiency. Serum concentrations of AT may also be helpful together with the phenotype to distinguish individuals who are homozygous for the Z allele from SZ compound heterozygotes. In some cases phenotype determinations on the parents may be helpful in sorting out any confusion that arises from the combination of the AT level and phenotype.

The distinctive histologic feature of the disorder, periodic acid-Schiff-positive, diastase-resistant globules in the ER of hepatocytes substantiates the diagnosis. The inclusions are eosinophilic, round to oval, and 1-40µm in diameter. They are most prominent in periportal hepatocytes but also may be seen in kupffer cells and cells of biliary ductular lineage. However, the presence of these globules is not pathognomonic. Similar structures occasionally are observed in non-deficient patients with other liver diseases. The histologic picture is also characterized by variable degrees of hepatocellular necrosis, inflammatory cell infiltration, periportal
fibrosis, or cirrhosis. There is often evidence of bile duct epithelial cell destruction, and occasionally there is paucity of intrahepatic bile ducts.

**Treatment**

The most important principle in the treatment of AT deficiency is avoidance of cigarette smoking. Smoking markedly accelerates the destructive lung disease that is associated with AT deficiency, reduces the quality of life and significantly shortens the longevity of these individuals.

There is no specific therapy for AT deficiency-associated liver disease. Clinical care largely involves supportive management of symptoms resulting from liver dysfunction and the prevention of complications that are generic to all chronic and acute liver diseases. Although ursodeoxycholic acid and colchicine have been mentioned in the literature there is no evidence for biochemical or clinical efficacy of either of these drugs.

Progressive liver dysfunction and liver failure in children has been treated by orthotopic liver transplantation with survival rates well over 90% at 1 year and 80% at 5 years. However, the slow progression of liver disease in this disorder (see Clinical Manifestations and Prognosis sections above) must be carefully considered in the decision to undertake liver transplantation. Children with AT deficiency and mild liver dysfunction (elevated transaminase levels and/or hepatomegaly) without functional impairment may never need liver transplantation.

A variety of other approaches to therapy or prevention of liver and lung disease have been proposed and, in some cases, are being investigated. This includes the use of generic and specific chemical chaperones, mechanism-based pharmacological strategies such as cyclosporine A to prevent mitochondrial dysfunction, cell transplantation therapies and gene transfer techniques that can repair the mutant gene.

**Prognosis**

Approximately 50 children with AT deficiency undergo liver transplantation each year in the US and it is the most common genetic diagnosis for liver transplantation in children. However, it is still not clear what clinical manifestations or abnormal laboratory test results can be used to predict a poor prognosis for children affected by this disorder. Persistence of hyperbilirubinemia, hard hepatomegaly, early development of splenomegaly, elevated aminotransferase levels, progressive prolongation of the prothrombin time, lowered trypsin inhibitory capacity have all been mentioned in the literature as harbingers of poor outcome. However, some have had the experience of children with this liver disease leading relatively normal lives for
years after the development of hepatosplenomegaly and mild prolongation of the prothrombin time. In one study of 44 patients seen over a 16-year period at St Louis Children's Hospital, 17 had cirrhosis or portal hypertension. Nine of these 17 patients had a prolonged and relatively uneventful course for at least 4 years after the diagnosis of cirrhosis or portal hypertension. Two of these eventually underwent liver transplantation, but the other seven led relatively healthy lives for up to 22 years after that. These nine patients could be distinguished from the remaining eight only by overall life functioning and not by any single clinical or biochemical characteristic. There are other reports of children with classical AT deficiency surviving with relatively normal overall life functioning for more than 10 to 15 years despite fairly significant liver dysfunction. Hence predictions of poor prognosis and for timing of liver transplantation depend more on overall life functioning of the affected child than on histologic or laboratory analysis.

**Genetic Counseling**

Restriction fragment length polymorphisms detected with synthetic oligonucleotide probes and family studies allow prenatal diagnosis of AT deficiency. Nevertheless, it is not clear how prenatal diagnosis for this deficiency should be used and how families should be counseled once the diagnosis is made. Current data indicating that 90-92% of persons affected by AT deficiency escape liver disease, at least up to the mid-30s in age, and that homozygotes may not develop emphysema or even pulmonary function abnormalities altogether or at least until age 60-70 if they avoid cigarette smoking would support a counseling strategy in which amniocentesis and pregnancy termination are discouraged. There are 2 studies that are purported to address the risk for a second child with liver disease due to AT deficiency but they come to completely different conclusions and both studies are highly biased in ascertainment. So there is no real substantive data from which to advise parents either for or against the options of amniocentesis and/or pregnancy termination.

**ChiLDReN Network studies that include patients with Alpha-1**

The ChiLDReN Network has several studies that include patients with Alpha-1.

The LOGIC and FORCE studies are natural history studies that include patients with Alpha-1. A natural history study is aimed at acquiring information and data that will provide a better understanding of rare conditions. Participants will be asked to do such things as allow study personnel to obtain information from medical records and an interview, and to collect blood, urine, and tissue samples when clinically indicated, in order to understand the causes of these diseases and to improve the diagnosis and treatment of children with these
diseases. All of the information obtained in these studies is confidential and no names or identifying information are used in the studies.

**LOGIC:** A longitudinal study of genetic causes of intrahepatic cholestasis.

*Eligibility:* Children and adults ages 6 months through 25 years diagnosed with Alagille Syndrome, alpha-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis, or bile acid synthesis defects, both before and after liver transplantation.

[ClinicalTrials.gov Study NCT00571272](https://clinicaltrials.gov)

**FORCE:** A cross-sectional and longitudinal assessment of the utility of liver stiffness measurement (as assessed by elastography) in children with chronic cholestatic liver disease.

*Eligibility:* Children currently enrolled in BASIC, PROBE, or LOGIC with a diagnosis of biliary atresia, alpha-1 antitrypsin deficiency or Alagille syndrome.

[ClinicalTrials.gov Study NCT02922751](https://clinicaltrials.gov)

**Organizations or foundations that help families dealing with Alpha-1**

The ChiLDReN Network works with numerous groups that support patients and families who are dealing with rare liver diseases. Please [click here](https://children.org) to go to that page on our website (Information for Families). You will see the list of groups and information about them.