ADVANCES IN HEPATOLOGY

Current Research and Management Strategies in Alpha-1-Antitrypsin Deficiency Disorders

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G&H Could you briefly describe the pathophysiology of alpha-1-antitrypsin deficiency-related disease?

DP Alpha-1-antitrypsin (alpha-1-AT) is a protein normally secreted by the liver, the main function of which is the inhibition of neutrophil elastase. Alpha-1-AT deficiency occurs in people with a genetic variant in alpha-1-AT that results in altered folding of the protein. The variant alpha-1-AT Z is retained in liver cells and causes liver damage by a distinct mechanism because it has a tendency to aggregate. Diminished levels of alpha-1-AT in the blood and body fluids leave neutrophil elastase unchecked, and lung disease, specifically emphysema/chronic obstructive pulmonary disease (COPD), results from the destructive action of elastase on lung connective tissue.

There are two very important mysteries about this deficiency. First, we do not know why only 8% of the affected individuals develop clinically significant liver disease, an observation that is firmly established by the Swedish cohort study carried out by Sveger over the last 40 years. Extensive clinical experience has shown that there is also wide variation in the onset and severity of liver disease. These observations have led to the concept that genetic and environmental modifiers play a critical role in determining susceptibility to liver disease in alpha-1-AT deficiency. A second mystery is why it takes almost 30 years for COPD to emerge in the most severely affected form of the lung disease. We know that cigarette smoking is a major modifier of the lung disease, increasing the rate of onset and severity by thousands-fold, but we do not know the other genetic and environmental modifiers of lung disease and we do not know what protects the lungs during childhood, adolescence, and early adulthood.

G&H Has the mechanism for genetic variation leading to liver disease in alpha-1-AT deficiency been identified?

DP I do not believe that any specific variants have yet been pinpointed. Our current belief is that there are several, if not many, genetic variations or modifiers that can increase or decrease susceptibility to this liver disease. Several specific modifiers have been recently proposed, including a single-nucleotide polymorphism in the upstream flanking region of the antitrypsin gene itself. Possibly more promising is a single-nucleotide polymorphism affecting a mannosidase in the endoplasmic reticulum (ER), which fits with our current theory that the quality control apparatus of the cell will be a target of modifiers that predispose to liver disease in this condition. Quality control, in this case, refers to mechanisms by which the cell will dispose of the abnormal protein. In the majority of patients with the alpha-1-AT deficiency, this mechanism seems able to clear the mutant protein. A polymorphism affecting ER function might result in greater hepatic accumulation of the mutant protein and thereby more hepatic toxicity. However, on the basis of the data that have been provided so far, I doubt that these two polymorphisms will withstand further, more stringent testing of their validity.

Our current hypothetical model for pathobiology of liver damage envisions genetic and environmental modifiers that affect the folding and polymerization of alpha-1-AT and other aggregation-prone proteins or affect how hepatocytes dispose of them. These are mechanisms that are fundamentally important for any kind of disease involving an aggregation-prone or a misfolded protein, which include not just liver diseases but some of the most common neurodegenerative disorders. The regulation of
proteotoxicity (ie, cells’ capacity to handle protein toxicity) has also been recognized as fundamental to longevity of the cell, longevity of the tissue, and longevity of the organism as a whole. Indeed, all of the pathways we are researching in relation to alpha-1-AT deficiency are fundamentally important for survival and longevity.

**G&H How often is alpha-1-AT deficiency at the root of neonatal liver dysfunction?**

**DP** Neonatal patients with prolonged jaundice are lumped into the category of neonatal hepatitis syndrome, which has many different potential causes. Of those, alpha-1-AT is one of the most common genetic causes. Relatively crude epidemiologic data suggest that 20–25% of neonatal hepatitis/cholestasis is due to biliary atresia, 20% to alpha-1-AT deficiency, and the remaining 50–55% to a variety of disorders, each in smaller proportions.

**G&H How does alpha-1-AT deficiency-related liver disease generally present in pediatric patients?**

**DP** Often, a child with the deficiency will present at 4 weeks of age with prolonged jaundice. In most cases, they will go on to clear the jaundice by 1 year of age and never develop clinically significant liver disease. However, approximately 8–10% will develop liver disease, although it is very hard to predict who those will be. This is another reason why understanding the genetic and environmental modifiers is so important. Without that understanding and predictive ability, we can only tell families that their child has the deficiency but that we cannot predict whether or not they will go on to develop liver disease that requires liver transplantation.

**G&H How do you follow neonatal patients who have been identified as having the deficiency?**

**DP** These patients need to be followed on a yearly basis for quite a long time. It is not uncommon for a neonatal patient to present with jaundice and elevated serum transaminase and bilirubin levels. By the time they are 1 year old, all of the symptoms may have resolved and they might enter a symptom-free honeymoon period. However, after a few years of follow-up, their liver enzymes and bilirubin levels may gradually increase, they may develop an enlarged spleen or liver, or they may develop portal hypertension.

**G&H What are the therapeutic options for patients who have developed alpha-1-AT deficiency-related disease?**

**DP** Progressive liver disease from alpha-1-AT deficiency is generally handled in the same way we handle other childhood liver diseases. The focus is on providing support to the patient to prevent the complications, including gastrointestinal bleeding, hypersplenism, ascites, spontaneous bacterial peritonitis, encephalopathy, and fat-soluble vitamin deficiency. Ultimately, these patients may require transplantation for decompensated liver function.

Another issue in pediatric patients is growth failure, which is a general effect of pediatric liver disease. In some cases, diet must be supplemented enterally or parenterally. Pediatric patients with liver disease are also more susceptible to systemic infections and require close monitoring and access to relatively rapid evaluation and treatment at a tertiary care facility.

Aside from the complications of portal hypertension and infection, I counsel patients and their families from a very early age to avoid cigarette smoking. This has nothing to do with the development of liver disease, but it increases the likelihood of COPD for adults by thousands-fold and must be avoided in patients with this condition.

**G&H What are the challenges in studying patients with alpha-1-AT–related liver disease?**

**DP** It is very hard to identify the relevant modifiers through human studies because they require the participation of many affected families. Approximately 200 families with more than one member affected by both the mutant protein and the liver disease are needed. Another way to study the deficiency is through mouse breeding, which is time-consuming. In my own work in collaboration with Drs. Stephen Pak and Gary Silverman, we have generated a novel *Caenorhabditis elegans* model of antitrypsin deficiency. *C. elegans* breeding allows for high throughput screening, utilizing RNAi libraries, that can identify within months genes and pathways that are potential modifiers. We know that many of the genes in *C. elegans* are shared with mammals, and we know that once specific genes that alter the phenotype in *C. elegans* are identified, they can then be tested more easily and more quickly in mouse models and in human population studies.

**G&H How has the understanding of alpha-1-AT deficiency led to new therapeutic targets and research to treat protein toxicity and prevent liver disease from this disorder?**

**DP** A variety of strategies are currently under investigation. Because the variant protein retains at least some of its functional activity, a strategy that enhances its release from hepatocytes in the blood and body fluids has the potential to ameliorate both liver and lung disease in alpha-1-AT deficiency. There is exciting research underway on a class of drugs called pharmacologic chaperones that presumably alter the folding of variant proteins in...
such a way that it improves their capacity to traverse the quality control apparatus within the secretory pathway.

Another class of drugs being explored is the so-called proteostasis regulators. These drugs presumably alter the folding landscape of the cell in a general way that favors the secretion of variant proteins like the one that causes alpha-1-AT deficiency. Some groups are investigating the possibility of using peptide fragments that can bind to the variant protein as a chemical basis for developing drugs that are specific folding agonists.

There is also exploration of strategies specifically designed for the liver disease in alpha-1-AT deficiency that would not be expected to affect the lung disease, including strategies that would enhance hepatic disposal of the variant protein or inhibit its synthesis. In the first scenario, a drug might enhance the known pathways by which an abnormal protein is degraded in a cell, a strategy that my group is currently exploring. Strategies to inhibit synthesis of the protein such as antisense oligonucleotides and short interfering RNA are also being investigated.

Finally, there is the potential for cell transplantation therapy. The idea behind cell transplantation therapy in alpha-1-AT deficiency is that damaged endogenous liver cells will elicit the regenerative signals that facilitate the replication of transplanted healthy cells by what is called a “selective proliferative advantage.” All of these ideas have potential and are in varying stages of development.

**G&H** Do you envision future therapies as requiring lifelong administration in affected patients?

**DP** We know that approximately 90% of the population with alpha-1-AT deficiency protects themselves through endogenous mechanisms. One could envision that a drug that enhances those mechanisms and pathways, even modestly, for periods of time, could protect the other 10% of patients. Therefore, the new therapies that are under investigation have the potential to work with intermittent dosing. The biggest problem that we are going to have, once these therapies are available, is that we have no way to predict which deficient patients are likely to have progressive disease and so we will either need therapies that have a wide margin of safety or that are effective after the liver disease has evolved.

**G&H** Can you explain the link between alpha-1-AT deficiency and the development of cancer?

**DP** We know that adults with alpha-1-AT deficiency are more likely to develop hepatocellular carcinoma as well as cholangiocarcinoma. Patients may even present initially with these malignancies, which are then traced back to alpha-1-AT deficiency without any other clinical indicator of liver disease. In some cases, there is also no history of a previous problem with the liver or of prolonged jaundice in the newborn period. These are presumably patients affected by some dominant modifier or set of environmental and/or genetic modifiers that protect them from liver disease until late in life.

The mechanism by which deficiency predisposes to hepatic malignancy is not completely understood. I have proposed a theory that involves cross-talk between the hepatocytes with greater accumulation of the mutant antitrypsin (the so-called globule-containing hepatocytes) and the globule-devoid hepatocytes that have lesser accumulation of aggregated mutant antitrypsin. The globule-containing hepatocytes are termed “sick but not dead” and are therein impaired in proliferation and in death. The theory envisions these cells as chronically expressing some regenerative activity that stimulates the adjacent globule-devoid hepatocytes in trans. These globule-devoid hepatocytes are relatively healthy and therefore have a selective proliferative advantage. Chronic proliferation in the presence of tissue damage leads to neoplasia.

**G&H** Beyond therapeutics, are there other areas of research that are important for future treatment of patients with alpha-1-AT deficiency?

**DP** We need to develop better prognostic indicators to determine who among our patients are going to develop disease in the long term. This will be particularly important as therapeutic options become available, and we need to identify patients who require treatment. Prognostic information is going to come from identification and increased understanding of the endogenous modifiers that process mutant proteins. I am very excited about the possibility of identifying these modifiers, through the focused pathobiologic research that is currently ongoing worldwide.

**Suggested Reading**


