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Alpha-1 Antitrypsin Deficiency: Pathogenesis, Clinical Presentation, Diagnosis, and Treatment

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ABSTRACT

Alpha-1 antitrypsin deficiency is an inherited disease affecting the lung and liver. The typical pulmonary manifestation is chronic obstructive pulmonary disease and emphysema. Severe chronic obstructive pulmonary disease may occur in young adulthood, and terminal respiratory insufficiency causes premature death in many patients. In the liver, alpha-1 antitrypsin deficiency may manifest as benign neonatal hepatitis syndrome; a small percentage of adults develop liver fibrosis, with progression to cirrhosis and hepatocellular carcinoma. The alpha-1 antitrypsin molecule is a serine protease inhibitor that is predominantly produced in the liver. Its most important physiologic functions are the protection of pulmonary tissue from aggressive proteolytic enzymes and regulation of pulmonary immune processes. Diagnosis of alpha-1 antitrypsin deficiency can be established by measurement of the serum alpha-1 antitrypsin concentration or by genetic analysis. Treatment is similar to the usual treatment for patients with chronic obstructive pulmonary disease. A further option is substitution therapy with human alpha-1 antitrypsin. The targets of treatment are the prevention of the accelerated decline of pulmonary function, reduction of lung infections, and improvements in exercise capacity.
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KEYWORDS: Alpha-1 antitrypsin deficiency; Alpha-1 protease inhibitor deficiency; Antiprotease; Chronic obstructive pulmonary disease; Liver cirrhosis; Lung emphysema; Neonatal hepatitis syndrome

Alpha-1 antitrypsin deficiency (alpha-1 protease inhibitor deficiency) is defined by a reduced concentration of alpha-1 antitrypsin in the serum and/or the identification of a defective genotype. It is not a rare disease, but it is one that is underdiagnosed.[1]

In the past few decades, extensive efforts have been made to understand the genetics and biology of alpha-1 antitrypsin, as well as the pathophysiologic mechanisms in alpha-1 antitrypsin deficiency. To date, however, major gaps and uncertainties remain in our understanding of the disease. The identification of patients and initiation of adequate treatment are important to delay or prevent severe lung damage and associated impairment of the quality of life.[2]

GENETICS AND BIOLOGY

Alpha-1 antitrypsin deficiency is an autosomal recessive disease. The *SERPINA1* gene (formerly known as *PI*), which encodes the alpha-1 antitrypsin protein, is 12.2 kb and located on the long arm of chromosome 14 (14q31-32.3). The gene is highly pleomorphic, and to date more than 100 allelic variants have been identified. The variants can broadly be classified according to their effects on levels of serum alpha-1 antitrypsin protein. The M alleles (M1 to M6) are the most common and are defined as "normal variants" because they are associated with normal serum alpha-1 antitrypsin protein levels. Disease manifestation is associated with null variants or genotypes resulting in impaired gene expression, translation, or protein synthesis. Typical genetically determined abnormalities in protein synthesis that result in alpha-1 antitrypsin deficiency are shown in Figure 1. The majority of individuals with lung or liver disease are homozygous for the alleles Z or S (ZZ and SS phenotype), or heterozygous for the 2 (MS, MZ, or SZ phenotype), all of which result in diminished serum alpha-1 antitrypsin levels.

Alpha-1 antitrypsin is a 52-kDa molecule (Figure 2) that is predominantly produced in the liver and released into the blood. The normal daily production is approxi-

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mately 34 mg/kg, and the physiologic serum concentration for adults ranges from 1.5 to 3.0 g/L (20-52 μmol/L). Under normal conditions, alpha-1 antitrypsin is constitutively produced and, as an acute phase protein, is upregulated during inflammation, infection, cancer, and pregnancy.

The most important physiologic function of alpha-1 antitrypsin is inactivation of released proteolytic enzymes in pulmonary tissue. The large surface of the lung is continuously exposed to a high burden of airborne pathogens, resulting in frequent cellular immune responses. During the resultant process of phagocytosis, proteases and oxidants are released into the adjacent lung tissue. The most important protease is neutrophil elastase, which has a high potential to destroy lung matrix components. Other common proteases with destructive potential are cathepsin G, plasmin activator, and proteinase-3.

In healthy humans, the lung is protected by a variety of antiproteases that quickly inactivate the proteases at a ratio of 1:1. Of the antiproteases in the lung, alpha-1 antitrypsin is present at the highest concentration and has the highest affinity for neutrophil elastase (10^7 M^{-1} s^{-1}). Alpha-1 antitrypsin belongs to the family of serine protease inhibitors, known as the serpins. Other important lung protease inhibitors with similar affinity to neutrophil elastase, but present at lower concentrations than alpha-1 antitrypsin, are secretory leukoprotease inhibitor (SLPI) and elafin.[3]

CLINICAL SIGNIFICANCE

- Alpha-1 antitrypsin deficiency is a common disease that is highly underdiagnosed.
- Measurement of the serum alpha-1 antitrypsin concentration or genetic analysis establishes the diagnosis.
- The majority of genetically affected individuals develop lung or liver disease, resulting in severe COPD and liver cirrhosis in young adults.
- Treatment of the lung disease is similar to treatment of smoking-related COPD. Substitution with plasma-derived alpha-1 antitrypsin should be performed in selected cases.

PREVALENCE

Caucasians of Europe and North America have the highest allele frequencies for alpha-1 antitrypsin deficiency globally.[4] Prevalence estimates for typical deficiency genotypes of the disease are presented in Table 1. In all countries, however, the number of clinically identified patients is far less than the anticipated prevalence based on allele frequencies. It is estimated that 10% to 35% of individuals with homozygous ZZ genotypes do not exhibit clinical symptoms.[5] The reasons underlying the lack of a direct relationship between the genotype and the phenotype are not understood.

In the United States, it is estimated that 60,000 patients have symptomatic alpha-1 antitrypsin deficiency, but fewer than 10,000 have actually been identified.[6] It is possible that large numbers of affected patients are misclassified as patients with bronchial asthma or smoking-related chronic obstructive pulmonary disease (COPD).

PATHOPHYSIOLOGY

In patients with the ZZ variant, alpha-1 antitrypsin proteins have a substitution of lysine for glutamic acid at position 342 of the amino acid sequence. This results in abnormalities in the tertiary structure of the molecule. Protein synthesis in the rough endoplasmic reticulum of hepatocytes is delayed so that approximately 85% of synthesized molecules polymerize into large conglomerates.[7] These polymers cannot be processed further and accumulate in the rough endoplasmic reticulum. Only a few nonpolymerized molecules are released into the blood. In individuals with the ZZ genotype, the antiproteolytic activity of alpha-1 antitrypsin against the most important substrate, neutrophil elastase, is approximately 5 times less than that of normal alpha-1 antitrypsin.[8]

In hepatocytes, continuous accumulation of alpha-1 antitrypsin molecules may result in cell injury and later in cell death. Patients with alpha-1 antitrypsin deficiency have a highly increased risk of liver fibrosis and cirrhosis. The amount of accumulated polymerized molecules correlates with the stage of the cirrhosis.[9]

Alpha-1 antitrypsin deficiency is often described as a storage disease of the hepatocellular endoplasmic reticulum. However, when one takes into account the better-known lysosomal storage diseases, alpha-1 antitrypsin deficiency may be better described as a conformational disease, similar to amyloidosis, because the reason for the storage is a change in peptide conformation rather than a functional deficit of cellular organelles.[10]

In patients with alpha-1 antitrypsin deficiency, the balance is disturbed between proteases and antiproteases in the lung. The majority of the released proteases remain active and slowly proceed to the destroy lung matrix components, alveolar structures, and blood vessels. Within a few decades, the progressive destruction results in chronic obstructive bronchitis and lung emphysema.[11,12]

In addition to its antiprotease activity, alpha-1 antitrypsin seems to have an important role in the regulation of inflammatory processes in the lung. The molecule itself has anti-inflammatory effects: It may inhibit immune responses, stimulate tissue repair and matrix production, and have antibacterial activities.[13]

Recent studies suggest that polymerization of ZZ alpha-1 antitrypsin molecules occurs not only within hepatocytes but also in peripheral tissues, for example, the lung. Bronchoalveolar lavage fluids from patients with the ZZ genotype have been found to contain large quantities of poly-