Best Practice & Research Clinical Gastroenterology 24 (2010) 629–633

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

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Alpha-1-antitrypsin deficiency

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Keywords:
Alpha-1-antitrypsin
Protease
Antiprotease
Liver disease
Chronic obstructive pulmonary disease (COPD)

Alpha-1-antitrypsin deficiency (AATD) is a rare genetic disorder associated with the development of liver and lung disease. AAT is a 52-kD glycoprotein, produced mainly by hepatocytes and secreted into the blood. Agglomeration of the AAT-protein in hepatocytes can result in liver disease. Exposure to smoke is the major risk factor for the development of lung disease characterised as early chronic obstructive lung disease (COPD). Diagnosis is based on the analysis of the AAT genotype and phenotype. The measurement of the AAT serum level is useful as screening test. Liver biopsy is not necessary to establish the diagnosis. Therapy for AAT-related liver disease is supportive, a specific therapy is not available. AATD is a rare condition (1:5000–10000) and, as a consequence, data and information on diagnosis and treatment are not easily accessible. This chapter provides a comprehensive overview on AATD, covering basic biology, diagnostic and therapeutic approaches.

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Introduction

Alpha-1-antitrypsin (AAT; also referred to as alpha$_1$ proteinase inhibitor (α_1-PI) is a 52-kD glycoprotein produced in hepatocytes and in smaller quantity in phagocytes and lung epithelial cells. The protein is 394 amino acids in size, the methionine at position 358 represents the active site. The protein is encoded by the protease inhibitor (Pi) locus on chromosome 14q32.1. The gene is called *SERPINA1* and is 12.2 kb in length with four coding exons, three non-coding exons, and six introns. More than 200 genetic alterations of *SERPINA1* are known with the Z and S mutation being the clinically most relevant

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doi:10.1016/j.bpg.2010.08.006

mutations. [1] Most patient with clinical manifestations of AATD are diagnosed with the type Pi ZZ (Pi = proteinase inhibitor). The Z mutation is a single nucleotide exchange resulting in an amino acid substitution at position 342 ($Glu^{342}Lys$). The Z mutation causes a conformational change in the encoded protein resulting is misfolding and subsequent formation of polymers, which can form inclusion bodies in hepatocytes. Calculations indicate that 116 million carriers and 1.1 million individuals with severe AATD exist worldwide. [2] A guideline published by the American Thoracic Society and the European Respiratory Society (ATS/ERS) in 2003 summarised current recommendations regarding the diagnostic procedures and therapy. [3]

Pathophysiology

The Z mutations and a number of other mutations (e.g. M Duarte or M Malton) are associated with liver disease, however, the wide range of clinical manifestation of individuals with Pi ZZ implies a role for environmental and genetic disease modifiers. Liver disease is generally found in homozygous Pi ZZ individuals and rarely in Z heterozygote individuals. Low serum level caused by null genes is not associated with liver disease. [4,5]

During synthesis, the mutant Z gene is appropriately transcribed, however, in the ER the mutant Z protein molecule is assembled inefficiently. [6] The mutant Z protein aggregates and forms large polymers. [4,7,8] Cellular systems involved in the 'quality control' of newly produced proteins, recognise these molecules as abnormal and induce their degradation. This quality control steps resulted in the degradation of most of the intracellular Z protein molecules and, thus, decreased release into the blood.

Polymerisation is a critical step in the disease pathophysiology. The reactive site of the AAT molecules binds to neutrophil proteases associated with a conformational change in the protein. The Z mutation causes a single amino acid substitution located at the reactive site and alters the conformational flexibility of the molecule. The Z mutation and the molecular consequences cause an aggregation of individual AAT molecules in a row. [5]

The altered synthesis and chaperone binding induce that the molecule is retained in the hepatocytes and directed to a degradation apparatus. The polymerisation likely plays a critical role in the perpetuation of the accumulation. Several intracellular pathways for protein degradation have been identified and are likely involved in these processes: ubiquitin dependent and ubiquitin independent proteasomal pathways, and autophagy.

The accumulation of mutant Z protein in the liver is not distributed evenly. Not all hepatocytes synthesise AAT [9] and some hepatocytes synthesise the mutant Z protein, but large intracellular accumulations do not occur.

The S mutation is the second mutation with significant clinical relevance. The S protein alone is retained intracellularly and polymers of the S protein do not form. When coexpressed with Z AAT, S/Z heteropolymers form, explaining why SZ patients can develop liver disease identical to homozygous ZZ patients.

Subsequent to the accumulation of polymerised AAT in hepatocytes and detection of these polymers by cellular mechanisms, liver damage develops. Z protein accumulation is associated with mitochondrial injury and with signalling of apoptosis through mitochondria, including cytochrome c release. Also autophagy pathways are activated subsequent to polymer aggregation. The continuous cellular stress and subsequent repair leads to liver fibrosis, cirrhosis, and chronic organ injury. Many factors such as systemic inflammation, toxic substances, and infections act as a 'second hit' and impact on this slowly progressing organ damage. These factors could increase Z protein synthesis with increased Z protein accumulation and liver injury.

Laboratory diagnosis

AATD is significantly underdiagnosed and diagnosis is often delayed for several years. This is caused by the rare incidence of the condition and its unspecific symptoms. The most common symptoms at first presentation are nonspecific: liver disease of unknown cause, dyspnoea, wheezing, cough, and bronchitis. [10,11] More than 100 different genetic variants have been identified, however, 95% of all clinically relevant cases have the Pi ZZ genotype. [12]

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