

Alpha-1-Antitrypsin Deficiency - AAT

Clinical Background

Alpha-1-antitrypsin (AAT, alpha-1-protease inhibitor) is the major protease (trypsin, chymotrypsin and elastase) inhibitor in human serum. The loss of this protease inhibitor increases the risk for developing emphysema in early adulthood.

Epidemiology

- Prevalence
 - Estimated that 2-3% of 2-3 million patients with chronic obstructive pulmonary disease (COPD) in the U.S. have AAT deficiency
 - 1/3,000 for severe deficiency
- Age – 30s-40s with early-onset COPD
- Ethnicity – highest prevalence in Caucasians of North American and European descent

Risk Factors

- Genetics
 - Over 100 AAT allelic variants have been classified according to their electrophoretic mobility using isoelectric focusing; most have no clinical significance
 - Common phenotypes include: MM, MS, SS, MZ and ZZ, associated with 100, 80, 60, 57.5 and 15% AAT activity, respectively
 - MM, present in 95% of Caucasians, is considered the normal phenotype
 - 95% of deficiency alleles in the general population are either S or Z
 - Z allele is associated with severe liver and lung disease, and the S allele is associated with milder lung disease
 - Heterozygotes for a deficiency allele are only at slightly increased risk for AAT deficiency-related disorders
- Concomitant tobacco use increases the risk of emphysema and lowers the age of onset

Pathophysiology

- AAT is an acute phase reactant synthesized by the liver; its inherited deficiency is associated with liver and lung disease
 - Most important role is inhibition of protease neutrophil elastase
- Decreased quantities of AAT allow elastase to degrade lung parenchyma
- Hepatic disease is secondary to accumulation of unsecreted AAT in hepatocytes

Clinical Presentation

- Adults
 - Pulmonary – early onset emphysema (panacinar)
 - Hepatic – liver dysfunction, cirrhosis
 - Occurs more often in individuals with a Z allele
 - Hepatitis with jaundice
 - Chronic liver disease
 - Skin – panniculitis
 - Necrotic areas with spontaneous suppuration
- Neonates

- 10% of affected newborns have hepatitis with cholestatic jaundice (prolonged jaundice with conjugated hyperbilirubinemia)
- Low AAT levels are also found in neonatal respiratory distress syndrome and severe protein-losing disorders
- Rare associated diseases
 - Wegener granulomatosis, necrotizing panniculitis, aneurysms of aortic and brain arteries
- Complications
 - Hepatocellular carcinoma and cholangiocarcinoma

Treatment

- Enzyme replacement treatment is available, so early diagnosis is crucial

Diagnosis

- Indications for testing
 - Adult with early-onset COPD (<45 years)
 - Necrotizing panniculitis (unexplained)
 - Sibling or family member with known AAT deficiency
 - Bronchiectasis without known etiology
 - Unexplained liver disease
 - Newborns with bleeding disorder or prolonged jaundice
 - ANCA vasculitis (anti-PR3 type)
- Laboratory testing
 - Initial testing – serum AAT concentrations usually low in disease
 - Because AAT is an acute phase reactant, it may be elevated
 - Plasma concentration can be elevated into the normal range in PI MZ heterozygotes
 - Up to fourfold increase observed in inflammatory conditions, cancer, and liver disease
 - Phenotyping and genotyping
 - Phenotype determination to identify AAT protein variants if concentration is <100 mg/dL
 - Molecular testing of *SERPINA1* (serpin peptidase inhibitor) gene for S and Z alleles

Differential Diagnosis

- Adults
 - Non-AAT COPD
 - Cirrhosis from other etiologies
- Pediatric
 - Viral infection
 - Hemochromatosis
 - Wilson disease
 - Autoimmune hepatitis
 - Inborn errors of metabolism

Screening

- Screening tests available prior to testing for levels
 - Pulmonary function studies (irreversible airflow obstruction)
 - Chest x-ray/CT scan

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Alpha-1-Antitrypsin & A1A Genotype with Reflex to Phenotype 0051256 Method: Immunoturbidimetric Polymerase Chain Reaction/Fluorescent Resonance Energy Transfer	Detects the presence of S and Z deficiency alleles and A1AT deficiency; includes reflex to phenotyping if A1AT concentration is not consistent with genotype 95% clinical sensitivity for DNA testing; 99% analytical sensitivity	An acutely ill AAT-deficient patient may have a falsely normal AAT concentration because AAT is an acute phase reactant	
Alpha-1-Antitrypsin Phenotype (includes Alpha-1-Antitrypsin) 0080500 Method: Isoelectric Focusing/ Immunoturbidimetric	Identifies AAT protein variants and AAT deficiency	An acutely ill AAT-deficient patient may have a falsely normal AAT concentration because AAT is an acute phase reactant	
Alpha-1-Antitrypsin 0050001 Method: Immunoturbidimetric	Detects AAT deficiency	An acutely ill AAT-deficient patient may have a falsely normal AAT concentration because AAT is an acute phase reactant	
Immunohistochemistry Stain Offering arup005 Method: Immunohistochemistry	For fixed tissue samples, consultative services as well as immunohistochemical staining for Alpha-1-antitrypsin (AAT) are available		

General References

Fairbanks KD, Tavill AS. Liver disease in alpha 1-antitrypsin deficiency: a review. *Am J Gastroenterol.* 2008; 103 (8) :2136-2141.

Fregonese L, Stolk J. Hereditary alpha-1-antitrypsin deficiency and its clinical consequences. *Orphanet J Rare Dis.* 2008; 3 :16-.

Hericks AJ, Bhat A. An overview of alpha-1 antitrypsin deficiency. *Mo Med.* 2007; 104 (3) :255-259.

Kohnlein T, Welte T. Alpha-1 antitrypsin deficiency: pathogenesis, clinical presentation, diagnosis, and treatment. *Am J Med.* 2008; 121 (1) :3-9.

Mulgrew AT, Taggart CC, McElvaney NG. Alpha-1-antitrypsin deficiency: current concepts. *Lung.* 2007; 185 (4) :191-201.

Navickis RJ, Wilkes MM. Update on research, diagnosis and management of alpha-antitrypsin deficiency.COPD. 2004; 1 (2) :279-292.

Rachelefsky G, Hogarth DK. Issues in the diagnosis of alpha(1)-antitrypsin deficiency.J Allergy Clin Immunol. 2008; :-.

Stolk J, Seersholm N, Kalsheker N. Alpha1-antitrypsin deficiency: current perspective on research, diagnosis, and management.Int J Chron Obstruct Pulmon Dis. 2006; 1 (2) :151-160.

Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency.Lancet. 2005; 365 (9478) :2225-2236.

Teckman JH, Lindblad D. Alpha-1-antitrypsin deficiency: diagnosis, pathophysiology, and management.Curr Gastroenterol Rep. 2006; 8 (1) :14-20.

References from the ARUP Institute for Clinical and Experimental Pathology®

Bornhorst JA, Calderon FR, Procter M, Tang W, Ashwood ER, Mao R. Genotypes and serum concentrations of human alpha-1-antitrypsin "P" protein variants in a clinical population.J Clin Pathol. 2007; 60 (10) :1124-1128.

Bornhorst JA, Procter M, Meadows C, Ashwood ER, Mao R. Evaluation of an integrative diagnostic algorithm for the identification of people at risk for alpha1-antitrypsin deficiency.Am J Clin Pathol. 2007; 128 (3) :482-490.

Slev PR, Williams BG, Harville TO, Ashwood ER, Bornhorst JA. Efficacy of the detection of the alpha1-antitrypsin "Z" deficiency variant by routine serum protein electrophoresis.Am J Clin Pathol. 2008; 130 (4) :568-572.

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Comprehensive Review: July 2009

Last Update: August 2009