

Alpha-1 Antitrypsin Deficiency (AATD)

Introduction

Deficiency of Alpha-1 Antitrypsin was first recognized in 1963. Six years after the initial observation an association between Alpha-1 Antitrypsin deficiency and lung disease in adults was recognized. A deficiency of this enzyme inhibitor was noted in some children with familial juvenile cirrhosis and cholestasis. Up to 35% of infants with hepatitis and jaundice may have Alpha-1 antitrypsin deficiency. A strong association between cigarette smoking and development of early onset panacinar emphysema with increased mortality has been observed in alpha-1 antitrypsin-deficient adults.

AATD is one of the most common genetic disorders to affect the Caucasian population. It occurs in 1-2.5% of Americans with chronic obstructive pulmonary disease (COPD), affecting a population of approximately 100,000 individuals.

Although common, it is under recognized - with frequent long delays (i.e. 7 years or more) between onset of symptoms and initial diagnosis - resulting in adverse medicine and quality of life effects. Educational effort must be expanded to enhance the practitioner's diagnostic suspicion of AATD and permit earlier diagnosis and attendant benefit. Educational efforts must include a patient/family component.

What is Alpha-1 Antitrypsin?

Alpha-1 antitrypsin is an amino acid glycoprotein produced by a single gene in the long arm of chromosome 14. It is synthesized and secreted predominantly by liver cells.


Alpha-1 Antitrypsin is responsible for 80 to 90% of serum trypsin inhibitory capacity but also inhibitory proteases, especially elastase. In the lung, its primary function is to inhibit neutrophil elastase and thereby prevent degradation of the connective tissue elements in the lung architecture. It protects against endogenous elastase-like enzymes released by stimulating neutrophils and alveolar macrophages.

Genetics and epidemiology

Alpha-1 antitrypsin gene alleles are inherited in autosomal codominant fashion and the alpha-1 antitrypsin PI phenotype is a result of a complete independent expression of two parental alleles. There are at least 75 known variants.

The vast majority is not clinically significant. The PI allele products (normal and deficient) are labeled (A through Z) corresponding to relative isoelectric focusing.

The normal PIM allele is the most common phenotype. PIM is found in 90% of individuals of European descent and alpha-1 antitrypsin levels are normal. Common alpha-1 antitrypsin variants include PIS and PIZ. The vast majority of individuals who are severely deficient in alpha-1 antitrypsin (less than 15% of normal level) are homozygous for the allelic variant PIZ and are designated PIZZ. Most of these PIZZ individuals are white; the PIZ alleles are rarely found in Black or Asian populations. The prevalence of PIZZ homozygous has been estimated between one in 1670 and one in 3500 in population of European Descent. This makes severe hereditary alpha-1 antitrypsin deficiency only slightly less common than cystic fibrosis.



Not all individuals severely deficient in alpha-1 antitrypsin with PIZZ phenotype experience significant clinical sequelae and decreased life spans. The actual percent is unknown, but it is thought to be as much as 5%. The reason for this may be related to environmental and other genetic factors including variations in expression of neutrophil elastase gene.

Alpha-1 Antitrypsin and Hepatic Disease

The mechanism of liver disease in alpha-1 antitrypsin deficiency is unknown. Hepatic damage could result from proteinase-antiproteinase imbalance.

Alpha-1 Antitrypsin and Lung Disease

Deficiency of alpha-1 antitrypsin accounts for 1 to 2% of all cases of emphysema in the United States. Cigarette smoking is the most important risk factor in development of early onset of emphysema in individuals with alpha-1 antitrypsin deficiency, most likely by increasing migration of neutrophils into the airways and increasing the number of macrophages, resulting in increased elastase activity.

In a normal individual, a balance is maintained between proteolytic enzymes and proteinase inhibitors.

Individuals not deficient in Alpha-1 Antitrypsin who develop emphysema secondary to cigarette smoke exposure have excessive elastase released by neutrophils, causing excessive degradation of alveolar walls seen in the common form of emphysema. In Alpha-1 Antitrypsin deficiency, even normal levels of neutrophil elastase if unchecked can lead destruction of the alveolar wall.

Alpha-1 Antitrypsin Pulmonary Disease in Adults

Adults that develop clinical respiratory manifestation of alpha-1 antitrypsin usually do so between ages 25 and 40 in patients who smoke and between 40 and 50 in nonsmokers. Presentation is a slow, progressive, severe panacinar emphysema manifested by progressive dyspnea. There may be chronic cough, acute and chronic bronchitis, bronchiectasis, and airway reactivity. Dyspnea in AATD patients is not different from that of emphysema patients without the deficiency, but significant symptoms and pathology occur 10 to 15 years earlier in alpha-1 antitrypsin deficient individuals who smoke (men and women are equally and similarly affected unlike persons who are not alpha-1 antitrypsin deficient).

The progressive decline in lung function is accentuated in alpha-1 antitrypsin deficiency. The obstructive lung disease associated with alpha-1 antitrypsin deficiency, if untreated by augmentation therapies, is progressive. Normal nonsmoking adults lose approximately 20 to 30 ml of pulmonary function from their FEV-1 each year. A smoker who is not alpha-1 antitrypsin deficient will lose 45 to 90 ml. Alpha-1 antitrypsin deficient patients who do not smoke will lose 80 to 100 ml of lung function from their FEV-1 each year and those who smoke lose more than 300 ml.

Diagnosis

The diagnosis of alpha-1 antitrypsin deficiency should be suspected in a number of clinical situations. About 35% of the cases of neonatal hepatitis are caused by such deficiency. Therefore, any infant with liver dysfunction should be evaluated.

Young adults with significant respiratory insufficiency and evidence of obstructive lung disease or individuals between ages 30 and 45 with chronic shortness of breath and coughing could have an alpha-1 antitrypsin deficiency. Clinically, significant dyspnea associated with abnormal lung function before the age of 45 in individuals who smoke should also prompt evaluation. AATD should be suspected in patients with recurrent pneumonia or pneumothorax. Emphysema not associated with cigarette smoking or family history of early onset of emphysema should also prompt an evaluation.

When serum levels of AAT are less than 35% of normal, more definitive testing should be performed along with family studies. Phenotyping will identify the patient's PI type.

Task Force

A task force was convened in 1998 under the auspices of the ATS and ERS to develop evidence-based recommendations for optimal care of patients with deficiency of Alpha-1 Antitrypsin.

The goal of the task force was to prepare and present for the medical and interested lay communities, the reasoned, current views of a large international group of experts regarding the current diagnosis and management of individuals with AAT deficiency.

The recommendation is genetic screening should be definitely pursued in patients who fit the clinical recognition.

We should follow the recommendations since they provide new insights that have impacted the clinical management of individuals with deficiency of AAT.

The main recommendations of the Alpha-1 Antitrypsin Deficiency Task Force included:

Clinical recognition

Evidence suggests that PIZZ AATD is frequently under recognized and/or misdiagnosed. The following features should prompt suspicion of the presence of AATD:

- Early onset emphysema (age 45 years or less)
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Antiproteinase three positive vasculitis (C-ANCA [antineutrophil cytoplasmic antibody] positive vasculitis)

- Family history of any of the following: Emphysema, bronchiectasis, liver disease and panniculitis
- Bronchiectasis without evident etiology

Genetic testing

For clinical purposes for which testing for AATD might be undertaken:

- Diagnostic testing (identify symptomatic or otherwise affected individuals)
- Predispositional testing: identify asymptomatic individuals at risk
- Assessment of carrier status in relation to reproduction
- Population screening

Diagnostic testing is recommended for:

- Symptomatic adults with emphysema, COPD or asthma with airflow obstruction incompletely reversible with aggressive treatment with bronchodilators
- Individuals with unexplained liver disease
- Asymptomatic individuals with persistent obstruction in PFTs with identifiable risk factors
- Adults with necrotizing panniculitis
- Diagnostic testing which should be discussed and could reasonably be accepted or declined
- Adults with bronchiectasis with evident etiology
- Adolescent with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factor
- Adults with C-ANCA positive vasculitis

Efficacy of Augmentation Therapy

- Intravenous augmentation therapy is recommended for individuals with established airflow obstruction with AATD. Evidence that such therapy is beneficial is stronger for patients with moderate airflow obstruction (i.e. FEV1 35-60% predicted)
- The task force recommended such therapy in patients who have undergone lung transplants and then have acute rejection episode or during an episodes of respiratory infection
- Not recommended for patients without emphysema

General Management

The task force recommended the usual management of a patient with emphysema, including bronchodilators, flu vaccine, pneumovax, oxygen, rehabilitation, antibiotics for infections, lung transplantation.

Liver Disease

Most PIZZ AATD individuals are clinically healthy throughout childhood but have abnormal liver function tests. This phenotype is a common cause of neonatal cholestasis. Cirrhosis has a peak incidence in elderly non-smokers who have not died from emphysema. The task force suggested that clinical management of individuals with AATD-related liver disease should include hepatitis A and B vaccinations, liver function tests and ultrasound examination on a regular basis. Liver transplantation is the only available therapy.

Other Conditions

There is a relationship between AATD, necrotizing panniculitis and C-ANCA positive vasculitis (Wegener's granulomatosis).

Conclusion

Earlier diagnosis of individuals with AATD will:

- Limit the psychosocial effects of delayed diagnosis
- Enable better management of pulmonary and hepatic diseases
- Promote more attention to smoking cessation
- Promote more attention to elimination of environmental irritants that would/could worsen pulmonary disease
- Initiation of Augmentation Therapy. A major effort is required to enhance clinicians' knowledge about AATD, with the goal that AATD individuals will receive an early diagnosis and receive optimal care

RAD recommends the following actions:

- Widespread distribution of the evidence-based standards for the diagnosis and management of individuals with AATD
- Every symposium presented on COPD should include information on AATD: diagnosis and treatment
- Develop and disseminate information through:
 - Lectures, teleconferences, web casts, grand rounds to enhance the awareness of primary care health providers
- Organize a national effort to enhance patient knowledge and to enable patients to be proactive in their care. Also, to educate patients with COPD and patients who smoke about the possibility they can have AATD
- More targeted genetic screening for at risk individuals



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