Grand Rounds Review

Suspecting and Testing for Alpha-1 Antitrypsin Deficiency—An Allergist's and/or Immunologist's Perspective

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Alpha-1 antitrypsin deficiency (AATD) is a hereditary, monogenic disorder with no unique clinical features. AATD can be difficult to diagnose as patients commonly present with respiratory symptoms often mistaken for other respiratory syndromes such as asthma or smoking-related chronic obstructive pulmonary disease. In addition, symptoms related to AATD may also affect other organs, including the liver, vasculature, and skin. The severity of AATD varies between individuals, and in severe cases, the irreversible lung damage can develop into emphysema. Early diagnosis is critical to enable the implementation of lifestyle changes and therapeutic options that can slow further deterioration of pulmonary tissue. Once AATD is suspected, a range of tests are available (serum alpha-1 proteinase inhibitor [A_1-PI] level measurement, phenotyping, genotyping, gene sequencing) for confirming AATD. Currently, intravenous infusion of A_1-PI is the only therapy that directly addresses the underlying cause of AATD, and has demonstrated efficacy in a recent randomized, placebo-controlled trial. This review discusses the etiology, testing, and management of AATD from the allergist's and/or immunologist's perspective. It aims to raise awareness of the condition among physicians who care for people with obstructive lung disorders and are therefore likely to see patients with obstructive lung disease that may, in fact, prove to be AATD. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

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CASE

JT was a 29-year-old man with increasing dyspnea on exertion. His medical history was obtained from his wife. He presented with dyspnea to an allergist 2 years earlier and was diagnosed with asthma. His wife recalls his symptoms starting a few years earlier with dyspnea during exercise. He was treated with albuterol, as needed, and a combination of a long-acting beta agonist and inhaled corticosteroid. She remembered him having intermittent wheezing on his allergist's exam. He never had a chest radiograph. His wife remembers his spirometry demonstrating asthma-like changes, but he never received complete pulmonary function testing or pre- or post-bronchodilator testing. He smoked less than a pack of cigarettes per day for a total of 11-pack-year history, but was never informed to stop smoking. He had no occupational exposures. He had a dog despite positive skin tests that suggested sensitivity to dogs. His wife stated that he had no other medical illnesses and had never experienced any liver disease. After 2 years of therapy, he died suddenly during sleep. His autopsy demonstrated emphysema. Autopsy diagnosis was alpha-1 antitrypsin deficiency (AATD) with hypoxia-induced arrhythmia.

ETIOLOGY AND PROGRESSION OF AATD

Elastin is an extracellular protein contributing to the elasticity of connective tissues and is a major component of the lung. During inflammation, activated neutrophils release various proteolytic enzymes, including neutrophil elastase (NE), to defend the body against infection. If left unchecked, NE also attacks the host connective tissue by degrading elastin. AATD is caused by decreased levels or function of the proteinase inhibitor alpha-1 antitrypsin (AAT; also known as alpha-1 proteinase inhibitor, A_1-PI), which arises as a consequence of mutations in a single gene (*SERPINA1*) located on chromosome 14.[1] A_1-PI is produced by the liver and plays an important role in the regulation of NE activity, irreversibly binding NE and targeting it for degradation. In A_1-PI-deficient individuals, insufficient A_1-PI levels lead to uncontrolled NE activity, which results in the progressive degradation of pulmonary tissue and contributes to the development of lung disease.[2,3] Because this tissue degradation mainly affects the small airways, especially at the level of the alveoli, the gas exchange function of the lung can be severely impaired. Individuals with AATD are often diagnosed with asthma or chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or bronchiectasis, and emphysema, which can become severe.[2,4-6] A_1-PI is released into the blood and tissues, and evidence suggests that it has multiple functions (including roles in immunity and inflammation) beyond its antiprotease activity.[7] Consequently, AATD

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Abbreviations used
A_1-PI- Alpha-1 proteinase inhibitor
AATD- Alpha-1 antitrypsin deficiency
COPD- Chronic obstructive pulmonary disease
CT- Computed tomography
FEV_1- Forced expiratory volume in one second
IV- Intravenous
NE- Neutrophil elastase

symptoms are not limited to the lung, and clinical features of the skin (eg, panniculitis), vasculature (eg, vasculitis), and liver (eg, cirrhosis) may also occur. In patients with AATD homozygous for the Z allele (ie, ZZ, see below for a description of the most common alleles), the abnormal protein accumulates in the liver, predisposing to hepatitis.[1,2,8,9]

AATD is a hereditary, autosomal, codominant, monogenic condition for which more than 500 single nucleotide polymorphisms have been identified, although not all of these have been validated.[3] The most common alleles include:

- M (normal allele)
- Z (leading to low A_1-PI levels, associated with severe AATD)
- S (leading to a mild decrease in circulating A_1-PI)
- Null allele (no detectable A_1-PI synthesis).[3]

Different allele combinations are associated with various levels of circulating A_1-PI. Individuals with only one defective allele might not present with clinical features of AATD, and not all individuals with 2 defective alleles are at the same risk of developing emphysema (Figure 1).[1,4,10-12]

The progression of lung disease in individuals with AATD is slow and symptoms such as cough or wheezing often appear only within the fourth and/or fifth decade of life, although they sometimes present earlier, during the second and/or third decade of life.[6] Because AATD leads to irreversible lung damage, it is crucial to identify patients at risk to enable early diagnosis and implementation of management and treatment strategies aimed at reducing the progression of lung disease.

UNDERESTIMATION AND MISDIAGNOSIS OF AATD

In the USA, the combined prevalence for the A_1-PI phenotypic classes SS, SZ, and ZZ has been estimated at 1/496.[13] Furthermore, 1 in 17 Americans have at least one allele associated with a degree of risk for AATD (ie, S or Z), and 1 in 6211 Americans are estimated to be homozygous for the Z allele.[13] The number of at-risk individuals tested in the USA was reported to have doubled between the years 2007 and 2010,[14] but despite this increase, AATD is still rarely diagnosed. Among the 100,000 individuals in the USA estimated to have AATD, fewer than 10% have been appropriately diagnosed.[15]

Respiratory symptoms in people with AATD include coughing, wheezing, excessive sputum production, and dyspnea, although these symptoms are also common to other respiratory diseases such as asthma and smoking-related COPD.[16] As a result, AATD is frequently misdiagnosed and this can result in long delays between the onset of symptoms and obtaining an accurate diagnosis of AATD. In a recent AATD support group held at Penn State University, the majority of patients first entered the health care system for their respiratory symptoms through visits with allergists and were treated for years, often with immunotherapy, before being referred and found to have AATD. Previous estimates put the average time from symptom onset to correct diagnosis of AATD at 7.2 years,[17] with numerous visits to different physicians being involved. A survey of 304 patients with AATD found that 44% had seen at least 3 physicians before they received an accurate diagnosis of AATD.[17]

WHEN TO SUSPECT AATD

Although AATD has no unique symptoms, there are clinical presentations that should raise suspicion (Table I). In particular, any individual with asthma with incompletely reversible airflow obstruction, as well as patients with COPD, should be tested, as suggested in a joint statement from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2003 (summarized in Table II).[1] In this statement, various recommendations are also proposed for other individuals, including the testing of asymptomatic adults with evidence of lung disease and smoking or occupational exposure, adults with necrotizing panniculitis, children or adults with unexplained liver disease, and bronchiectasis without apparent etiology. Testing should be considered for adults and adolescents with a sibling diagnosed to be homozygous for an AATD deficiency allele (eg, ZZ). As shown in Table II, the joint statement from the ATS/ERS indicates other situations in which testing may be required (eg, carrier testing) or is not recommended (eg, newborn screening).

To improve the diagnosis of AATD, physicians need to be aware of the disease, the testing recommendations, and what test is indicated for their patients. Allergists and/or immunologists, in particular, may see numerous patients with asthmatic symptoms and fixed or nonreversible obstruction, which in most cases is secondary to remodeling, but in some cases may be secondary to AATD.[18] Another population that allergists and/or immunologists treat is tobacco abusers. Most tobacco-induced respiratory symptoms in non-AATD patients generally appear at a later age (fifth decade of life or later), and such symptoms in younger-than-expected patients should promote further investigations to check for AATD.[19] Other suggestions of AATD include centrilobular and paraseptal emphysema associated with COPD. Panacinar emphysema may present mainly with basilar changes on chest radiographs or computed tomography (CT) lung scans; however, most patients with AATD present with both centrilobular and panlobular emphysema.[5]

AATD, COPD, and asthma share common signs and symptoms, but are different diseases that can be easily differentiated by quantifying serum A_1-PI levels and through phenotypic and/or genetic testing to identify A_1-PI protein and/or *SERPINA1* gene variants, respectively.[18]

DIAGNOSING AATD

As noted above, certain changes observed by radiography may suggest AATD. These include basilar predominance of emphysema.[5] Characterization of fixed obstructive disease by screening spirometry is an indication for further testing; in addition, spirometry should be used to assess the progression of lung disease. Full pulmonary function tests are expected to demonstrate obstructive disease, with the increase of residual volume and abnormal diffusion of carbon monoxide; however, similar changes are seen in non-AATD, tobacco-related COPD. When the changes noted above are discovered, A_1-PI serum level