

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 [A₁-PI] level measurement, phenotyping, genotyping, gene sequencing) for confirming AATD. Currently, intravenous infusion of A₁-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 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2015;3:506-11)

Key words: Alpha-1 antitrypsin deficiency; Asthma; COPD; Emphysema; Screening; Testing; Diagnosis

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, A₁-PI), which arises as a consequence of mutations in a single gene (*SERPINA1*) located on chromosome 14.¹ A₁-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 A₁-PI-deficient individuals, insufficient A₁-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} A₁-PI is released into the

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Abbreviations used

A₁-PI-Alpha-1 proteinase inhibitor

AATD-Alpha-1 antitrypsin deficiency

COPD-Chronic obstructive pulmonary disease

CT-Computed tomography

FEV₁-Forced expiratory volume in one second

IV-Intravenous

NE-Neutrophil elastase

blood and tissues, and evidence suggests that it has multiple functions (including roles in immunity and inflammation) beyond its antiprotease activity.⁷ Consequently, AATD 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 A₁-PI levels, associated with severe AATD)
- S (leading to a mild decrease in circulating A₁-PI)
- Null allele (no detectable A₁-PI synthesis).³

Different allele combinations are associated with various levels of circulating A₁-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 A₁-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 A₁-PI levels and through phenotypic and/or genetic testing to identify A₁-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

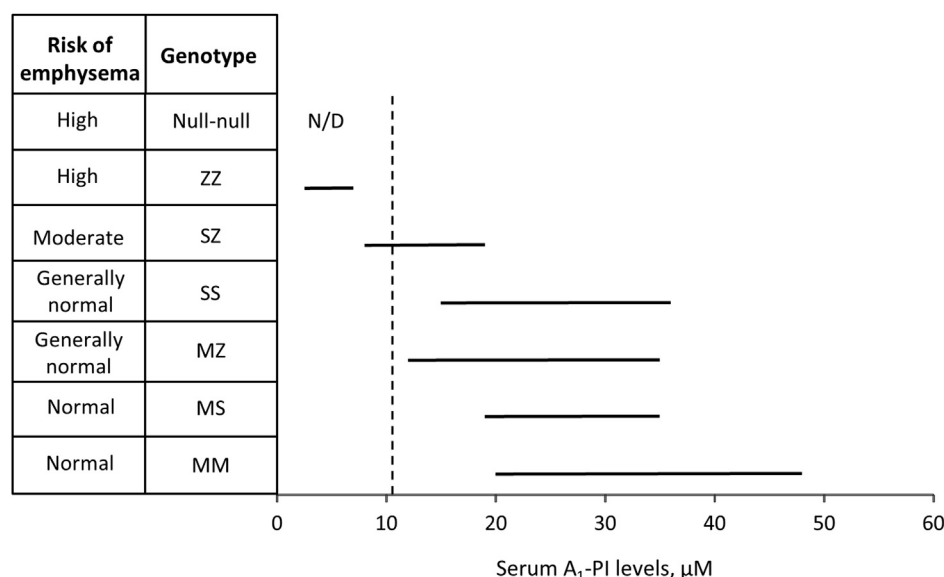


FIGURE 1. Relationships between AATD genotype, A₁-PI serum level, and risk of developing emphysema.^{1,4,10-12} Depending on their genotype, AATD patients present with various A₁-PI circulating levels and, therefore, are at different risks of developing emphysema. The dotted line denotes the historical A₁-PI threshold level (11 μM) below which patients are at an increased risk of developing emphysema. AATD, Alpha-1 antitrypsin deficiency; A₁-PI, alpha-1 proteinase inhibitor; N/D, not detectable.

TABLE I. Common and unique symptoms in AATD, asthma, and COPD

AATD	Asthma	COPD
Symptoms onset		
Fourth decade	Childhood	Fifth decade
Airway obstruction		
Nonreversible	Reversible in most cases	Nonreversible
Emphysema		
Panlobular (panacinar)	None	Centrilobular/paraseptal

AATD, Alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease.

and abnormal diffusion of carbon monoxide; however, similar changes are seen in non-AATD, tobacco-related COPD. When the changes noted above are discovered, A₁-PI serum level measurements should also be obtained and, in most cases, can confirm the diagnosis of AATD and allow further assessment of disease severity. When interpreting serum levels, it is important to note that A₁-PI is an acute phase protein whose serum levels can be artificially elevated during times of immune challenge (eg, infection).^{1,20} As a result, patients with AATD may present with normal or borderline A₁-PI levels, despite additional evidence of disease symptoms, and further testing should be considered (Table III).

Genotyping and phenotyping allow for the identification of the most well-known AATD variants, providing some indication of the severity of the deficiency. Phenotyping techniques such as isoelectric focusing can be used to determine the well-known serum A₁-PI protein variant(s). Genotyping provides qualitative information that can determine mutations in the *SERPINA1* gene and identify the more common A₁-PI deficiency alleles.

Standard genotyping tests are allele specific and are usually run with probes designed to target the Z and S alleles. If both of these alleles are absent, the genotyping result is recorded as MM, which means that nulls and other variants can be missed. In such cases, phenotyping can be more informative, as isoelectric focusing can allow for the identification of rare proteins. Furthermore, isoelectric focusing results may help to identify null alleles when combined with other tests such as A₁-PI serum level measurements.²¹ However, this technique is expensive, time consuming, and difficult to interpret compared with A₁-PI serum level quantification and genotyping. In addition to obtaining the above tests in commercial laboratories, testing kits with varying levels of sophistication are being offered free of charge by several manufacturers of A₁-PI replacement therapy preparations. Some of these kits provide serum levels and genotyping, whereas others are more comprehensive and also include C-reactive protein level measurement, phenotyping, and, when needed, genetic analysis using full gene sequencing, including promoter regions (next-generation sequencing).

MONITORING THE PROGRESSION OF LUNG DISEASE IN PATIENTS WITH AATD

Once a patient is diagnosed with AATD, the progression of lung disease is traditionally monitored by spirometry using forced expiratory volume in one second (FEV₁) as an indicator of the progression of lung airflow obstruction (Table III). Other spirometric parameters (eg, diffusing capacity of carbon monoxide) and records of number and severity of exacerbations are also useful tools to measure lung disease progression and response to therapy. CT densitometry enables the visualization and monitoring of the progression of emphysema and has been used in clinical trials as an alternative to spirometry. Lung CT has been shown to be 2.5 times more sensitive than conventional pulmonary function parameters and is recognized by the FDA as

TABLE II. American Thoracic Society/European Respiratory Society (ATS/ERS) criteria for screening and testing¹

Recommended	Should be discussed	Not recommended
Diagnostic testing—symptomatic individuals		
- Adults with persistent obstructive defects on pulmonary function tests and COPD, emphysema, or asthma (with incompletely reversible airflow obstruction) - Asymptomatic adults with evidence of lung disease and smoking or occupational exposure - Newborns, children, or adults with unexplained liver disease - Adults with necrotizing panniculitis	- Adults with persistent obstructive defects on pulmonary function tests and bronchiectasis - Adolescents with persistent obstructive pulmonary dysfunction - Asymptomatic adults with evidence of lung disease and no risk factors present for promoting AATD-related lung disease - Adults with multisystemic vasculitis (anti-PR-3-positive vasculitis)	- Adults without persistent obstructive defects on pulmonary function tests and asthma (with completely reversible airflow obstruction)
Predispositional testing—asymptomatic individuals		
- Adults and adolescents with a sibling homozygous for an AATD deficiency allele	- Adults and adolescents with an offspring, a parent or distant relative homozygous for and AATD deficiency allele - Adults and adolescents with a sibling, an offspring, a parent or distant relative heterozygous for and AATD deficiency allele - Adults and adolescents with a family history of obstructive lung disease or liver disease	- Neonatal testing
Carrier testing in the reproductive setting		
	- Adults and adolescents at high risk of having AATD-related diseases - Partners of individuals with AATD or carrier status	
Screening		
	- Adults or adolescents in countries where AATD prevalence and smoking rates are high (in the presence of adequate counseling)	- Newborns and adolescents - Healthy adults without increased risk of AATD - Smokers with normal spirometry

AATD, Alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; PR-3, proteinase-3.

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a meaningful method to monitor the progression of emphysema in research.²² It should be noted that its use in standard clinical practice is less clearly defined and current statements raise practical issues. These include the availability of equipment, the lack of expertise in analyzing and interpreting data, the cost, and the radiation dose received by the patient.²³

BEYOND DIAGNOSIS—MONITORING AND EFFECTIVE MANAGEMENT OF AATD

Early and correct diagnosis of AATD can enable appropriate and effective management of the disease (Table IV). Current management approaches mostly aim to alleviate AATD symptoms. Lifestyle modifications, such as smoking cessation, pollutant avoidance, healthy diet, and regular exercise, can be quickly implemented to maintain lung health and muscle mass and help prevent further respiratory complications. In addition, current pharmacological approaches involve the use of bronchodilators and anti-inflammatory therapy (inhaled corticosteroids) to relieve symptoms of airway obstruction and reduce inflammation. Early and aggressive use of antibiotics when patients present with respiratory infections may reduce the potential for lung damage. Vaccines such as the influenza vaccine, polysaccharide pneumococcal vaccine, and protein-conjugated pneumococcal vaccine should be administered to reduce the risk and severity of these infections. Oral corticosteroids should

be prescribed for patients with exacerbations. When appropriate, supplemental or long-term oxygen is also indicated,[†] and consideration for transplant is important in progressive cases. For ZZ individuals, liver transplant can be effective for both AATD-related liver and lung disease. For other AATD variants and for severe pulmonary disease in ZZ individuals, lung transplantation should be considered. However, because the long-term prognosis is poor post-lung transplant, appropriate therapies should be given early and aggressively to help limit progressive lung disease. Other approaches, including gene and stem cell therapies, are currently being investigated; the development of these methods is slowly progressing and might give rise to alternative treatments in the future.^{24,25}

Unlike lifestyle modifications or pharmacological management of AATD symptoms, intravenous (IV) A₁-PI administration is the only therapy that directly addresses the underlying deficiency of AATD. A₁-PI preparations are usually administered weekly by IV infusion at a dosage of 60 mg/kg of body weight. This dosage is considered sufficient to raise A₁-PI serum levels above 11 μM, a level historically considered to be the protective threshold, as serum levels below this have been associated with an increased risk of developing emphysema.^{1,20,26} Current commercially available, FDA-approved, A₁-PI products include Aralast NP and GLASSIA (Baxter, Ill), Prolastin-C (Grifols, Barcelona, Spain), and Zemaira (CSL Behring, Pa). The aim of augmentation therapy is to slow the destruction of lung tissue and, until last

TABLE III. Current methods to diagnose and monitor alpha-1 antitrypsin deficiency^{30,31}

Method(s)	Aim	Advantages	Disadvantages
A₁-PI quantitative testing			
- Nephelometry; radial immuno-diffusion; ELISA	- A ₁ -PI blood concentration assessment	- Widely available - Readily automated - Inexpensive - Reliable	- Cannot identify heterozygotes - A ₁ -PI is an acute phase reactant and its serum level can be artificially raised during infection/stress - Variation in daily A ₁ -PI circulating levels - Thresholds levels for each test vary and patients can present with borderline levels
A₁-PI qualitative testing			
- Isoelectric focusing	- A ₁ -PI phenotyping	- Can characterize patients' phenotype - Can identify heterozygotes - Semiautomated equipment available	- Time consuming - Experienced staff required to interpret results - Interpretation of rare alleles is difficult
- Allele-specific PCR	- A ₁ -PI genotyping	- Inexpensive - Conclusively identifies common mutations	- Does not detect null alleles - Limited number of probes - Rare mutations can be missed if not followed by next-generation sequencing
- Next-generation sequencing	- A ₁ -PI sequencing	- Can confirm genotyping results and detect novel, rare, and multiple mutations	- Expensive - Limited availability - Experienced staff required to interpret results
Pulmonary function monitoring			
- Screening spirometry	- Lung disease progression monitoring	- Widely available - Quick and easy to perform - Cost effective - May suggest diagnosis - Can confirm obstruction	- Day-to-day variability and wide normal ranges
- Full pulmonary function tests	- Overall lung function assessment - Degree of lung volume abnormality and diffusion of CO assessment	- Determines degree of diffusion abnormality - Allows assessment of total lung volume and residual volume	- Limited availability
Pulmonary qualitative monitoring			
- CT scanning	- To assess pulmonary densitometry	- Provides a sensitive and accurate assessment of lung density - Reliably indicates lung disease progression	- Expensive - Limited availability - Experienced staff required

A₁-PI, Alpha-1 proteinase inhibitor; CO, carbon monoxide; CT, computed tomography; PCR, polymerase chain reaction.

TABLE IV. Current available therapeutic approaches to manage alpha-1 antitrypsin deficiency

Therapy	Aims
Lifestyle modifications	
- Smoking cessation - Environmental risks avoidance - Nutritional follow-up - Pulmonary rehabilitation - Exercise	- Preserve lung health - Improve the patient's quality of life
Asthma and COPD pharmacological management	
- Inhaled bronchodilators - Inhaled steroids - Antibiotics - Oral corticosteroids - Oxygen therapy - Influenza vaccine - Pneumococcal vaccine both conjugate and polysaccharide as per guidelines	- Improve symptoms of airway obstruction - Relieve/slow down lung tissue destruction - Prevent infections
Augmentation therapy	
- Intravenous purified A ₁ -PI	- Reduce the rate of lung tissue destruction - Slow the progression of respiratory decline - Delay time to terminal respiratory event

A₁-PI, Alpha-1 proteinase inhibitor; COPD, chronic obstructive pulmonary disease.

year, efficacy had only been suggested by several observational studies and 2 small randomized controlled pilot trials (RCTs).^{27,28} These pilot RCTs showed no difference in the decline of FEV₁ between treated and control patients; however, a trend was observed for the reduction of lung density decline in the treatment group. These observations called for further investigations. The results of the recently completed Randomized, placebo-controlled trial in Alpha-1 Proteinase Inhibitor Deficiency (RAPID, NCT00261833), which followed 180 patients (93 treated and 87 placebo) over 2 years, provide evidence that IV A₁-PI augmentation therapy significantly slows the progression of emphysema in individuals with severe AATD. Results from this trial indicate that, compared with placebo, A₁-PI therapy delays time to terminal respiratory event (lung transplantation or death) and reduces overall progression of emphysema in patients with AATD and emphysema.²⁹

CONCLUSIONS

As allergists and/or immunologists, we see numerous patients with asthma, in particular, patients with severe asthma and abnormal FEV₁ thought to be secondary to remodeling. However, another potential cause of fixed obstructive airway disease is AATD, and screening patients for AATD could identify some of the 90% of individuals with AATD who are not yet diagnosed,¹⁵ which enables the implementation of appropriate care. The aim is that in the future the diagnosis of AATD will be made by the allergist and/or immunologist early in the disease, and appropriate therapy initiated to prevent progression of the lung damage. Patients with atypical asthma, with fixed airway obstruction or a family history of early COPD or unexplained COPD, should be screened for AATD. This should enable early diagnosis and effective management of AATD to decrease morbidity and premature mortality associated with this condition.

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