

Issues in the diagnosis of α_1 -antitrypsin deficiency

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α_1 -Antitrypsin deficiency is a relatively common genetic disease that is underrecognized and underdiagnosed. Early diagnosis in the asymptomatic patient helps modify lifestyle choices to reduce the risk of emphysema. In 2003, the American Thoracic Society and the European Respiratory Society issued guidelines to improve standards in diagnosing α_1 -antitrypsin deficiency. This review highlights key recommendations for diagnosis of α_1 -antitrypsin deficiency, including the different types of diagnostic tests recommended in the guidelines. Options for patient treatment will be discussed. (J Allergy Clin Immunol 2008;121:1183-1188.)

Key words: α_1 -Antitrypsin deficiency, augmentation therapy, genetic testing, diagnosis

α_1 -Antitrypsin deficiency (AATD), first described in 1963, is characterized by low levels of serum α_1 -antitrypsin (AAT).¹ AAT protects lung elastin from degradation by neutrophil elastase, a serine proteinase. The genetic defect of AATD leads to low plasma and alveolar concentrations of AAT. This is associated with progressive, severe, and life-threatening pulmonary emphysema.²

Life-threatening liver disease is another possible consequence of AATD. AAT is principally produced by hepatocytes. The most common inherited AAT defect (the Z variant) results in accumulation of abnormal protein in these cells.³ The accumulation of excess AAT can lead to cellular congestion and destruction, with possible development of severe liver disease and organ failure.²

AATD is one of the most common potentially fatal genetic diseases in the white population, with a similar prevalence to cystic fibrosis.⁴ Worldwide, it is estimated there are 117 million carriers and 3.4 million affected individuals.⁵ AATD has been reported in almost all regions of the world, including sub-Saharan Africa, Europe, North America, Asia, Australasia, and the Middle East.⁵ If targeted screening tests for AATD were to be performed on the estimated 19.3 million white patients with chronic obstructive pulmonary disease (COPD) in the United States, a projected

Abbreviations used

A1-PI: α_1 -Proteinase inhibitor
AAT: α_1 -Antitrypsin
AATD: α_1 -Antitrypsin deficiency
ATS: American Thoracic Society
ERS: European Respiratory Society
COPD: Chronic obstructive pulmonary disease
IEF: Isoelectric focusing
LVRS: Lung volume reduction surgery
PI: Protease inhibitor

1.29 million new patients with AATD would be identified.⁶ Despite this prevalence, AATD still remains greatly underrecognized and underdiagnosed, with estimates that only 5% of cases have been identified in the United States.⁷

Around 100 different genetic variants of AAT have been identified, and the most common are shown in Table I.⁸ AAT genotypes that confer an increased risk for emphysema contain deficient or null alleles combined in homozygous or heterozygous states and result in an AAT plasma level less than the relative protective threshold of 11 $\mu\text{mol/L}$.⁹ Patients with ZZ, Z-null, or null-null phenotypes are at high risk of emphysema, whereas those patients with MM and SS phenotypes have the same risk of emphysema as the general population. Patients with SZ phenotypes are at mild risk of emphysema, with only a small proportion having AAT levels less than the threshold of 11 $\mu\text{mol/L}$.⁹ The Z allele is associated with a severe form of AATD. Ninety-five percent of patients with a clinically relevant deficiency have the ZZ (homozygous) genotype, although patients with heterozygous Z genotypes (eg, MZ) can also exhibit clinically relevant deterioration in lung function and morbidity.^{4,10}

Guidelines for diagnosing AATD were published in 2003 by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) and are summarized in Fig 1.³ This review will discuss the clinical presentation of AATD, highlighting the symptoms and situations that should trigger suspicion of AATD by physicians. Criteria for diagnosis, recommended in the guidelines, will also be discussed. Treatment options for patients with AATD will be briefly considered.

IMPORTANCE OF EARLY DIAGNOSIS

Early diagnosis for the asymptomatic patient allows individuals to modify their behavior and lifestyle to reduce the risk of emphysema. This is particularly true for children. Most patients with AATD remain asymptomatic until their midteens or later. Smoking avoidance significantly decreases the likelihood of having symptomatic disease over a lifetime.¹¹⁻¹⁴ Three studies reported that providing information on AATD status to individuals identified at birth through neonatal screening programs reduced

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TABLE I. Most common phenotypes for AATD and the associated range of AAT serum levels*³

Phenotype	AAT concentrations		Emphysema risk compared with the general population
	μmol/L	mg/dL	
PIMM	20-48	150-350	No increase
PIMZ	17-33	90-210	No increase
PISS	15-33	100-200	No increase
PISZ	8-16	75-120	Mild increase
PIZZ	2.5-7	20-45	High risk
Null-null	0	0	High risk

*Serum levels are measured by using a typical commercial standard (in milligrams per deciliter) and the purified standard (micromoles) used in the United States.

smoking rates in these individuals. In the first study adolescents with AATD identified at birth had a significantly lower current and previous smoking rate compared with matched control subjects (current smoking rate: 6% vs 17%, $P < .05$; previous smoking rate: 6% vs 19%, $P < .05$).¹² In the second study patients identified as having PIZZ at birth had a lower rate of current smoking or of attempting to smoke compared with matched control subjects (current smoking rate: 4% vs 21%, $P = .10$; attempting to smoke rate: 27% vs 62%, $P = .02$).¹³ In the third study of 30-year-old patients with AATD identified at birth, significantly fewer lifetime smokers were identified among patients with AATD than among control subjects; 21% of subjects with PIZ, 23% of subjects with PISZ, and 34% of subjects with PIMM had smoked at some time ($P < .05$ compared with all patients with AATD).¹⁴ There is limited evidence that a diagnosis of AATD in current smokers results in increased smoking cessation rates. One recent investigation reported that smokers who were given a diagnosis of severe AATD were significantly more likely to report a 24-hour quit attempt than those with normal test results (59% vs 26%, $P < .05$).¹⁵ In the Alpha Coded Testing study of home testing for AATD, 12 (22.2%) of 54 subjects with PISZ and 6 (7.4%) of 81 subjects with PIZZ were still smoking 1 year after diagnosis of AATD.¹⁶

Early diagnosis allows health care professionals to monitor patients to ensure that the management of the disease is optimized.^{3,8} In addition, an early diagnosis can avert any adverse psychosocial effects associated with delayed diagnosis.¹⁷

Smoking is the most important risk factor for the development of emphysema in patients with AATD.^{3,18-20} Other risk factors for the development or progression of AATD-related diseases include passive smoking, occupational exposure to airway irritants, and specific environmental exposures, such as indoor kerosene heating or an agricultural occupation.²¹ Expert opinion recommends the following initiatives to minimize the risk of emphysema: smoking cessation, immunization against influenza and pneumococcal infection, reduced risk of breathing polluted air, and appropriate treatment of respiratory infection and atopic disease.^{4,22} Such initiatives are also supported by the current ATS and ERS guidelines.³

DIAGNOSTIC CHALLENGES

The average age of diagnosis for patients with AATD is 45.5 years, and around one third do not receive diagnoses until they are older than 50 years.⁷ Symptomatic patients might consult their physician on several occasions before an accurate diagnosis is made. In a survey of patients with AATD, 44% of patients saw at least 3 physicians before a correct diagnosis was made.¹⁷

There are no definitive physical symptoms that confirm AATD, although the ATS/ERS guidelines list clinical features that should prompt suspicion of this condition (Fig 1). A recent survey of patients given a diagnosis of AATD found that 81% of patients had COPD with symptoms of asthma, chronic bronchitis, and emphysema, usually in combination.²³ In a large study of the National Heart, Lung, and Blood Institute, the most common presenting symptoms of severe AATD were dyspnea on exertion (84%), wheezing (74%), cough (42%) and chronic bronchitis (8% to 40%).²⁴ In the National Heart, Lung, and Blood Institute registry, 61% of patients demonstrated bronchodilator reversibility on successive spirometric analysis. If the patient has progressed to emphysema, he or she will present with characteristics of increased respiratory work, airflow obstruction, and hyperinflation.

Patients are often initially given diagnoses of asthma because the early symptoms of AATD include cough, sputum production, and wheezing, and many demonstrate reversibility on spirometry. Eventually, dyspnea becomes the predominant symptom of AATD. A recent study of AAT levels of 458 established patients within pulmonary practices demonstrated abnormal levels in 15 patients; 57% of these patients were given diagnoses of asthma.²⁵

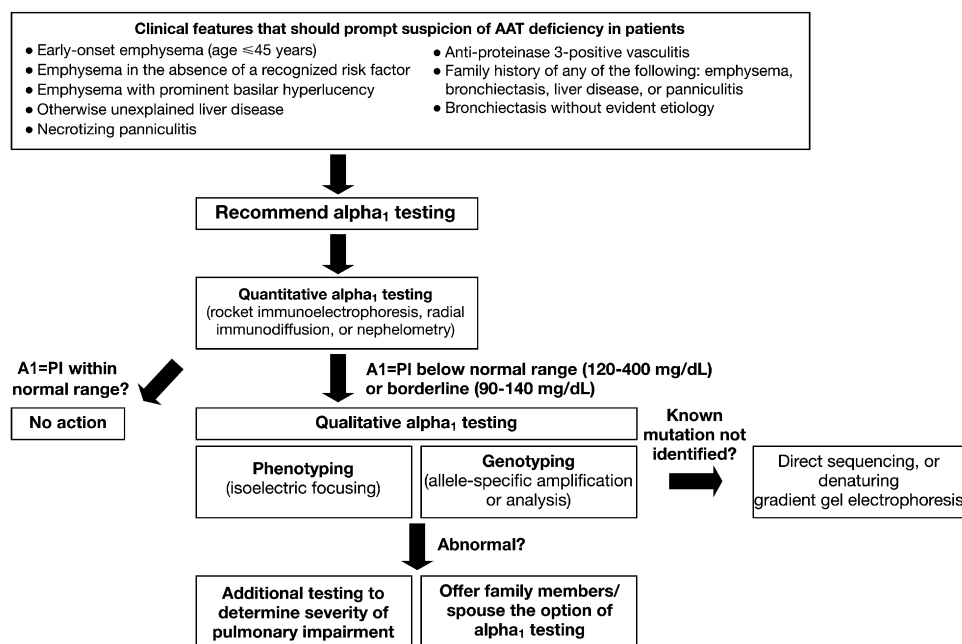
GUIDELINES FOR DIAGNOSIS

Testing for AATD can be performed to identify symptomatic subjects (diagnostic testing) or to identify asymptomatic subjects at high risk of AATD (predispositional testing).³ Diagnostic testing confirms the underlying cause of a specific medical condition. Predispositional testing allows for the identification of asymptomatic subjects who are at risk for AATD.

Identification of genotypes associated with AATD does not preordain the development of disease or symptoms. However, asymptomatic patients might have underlying physiologic abnormalities.²⁶ Environmental factors and genetic traits other than those linked to the protease inhibitor (PI) gene are also implicated in the pathophysiology of COPD.²⁷

The diagnosis of AATD can create psychologic burdens. The effect on the patient can depend on whether he or she is symptomatic or asymptomatic. In symptomatic patients there are positive and negative implications of a positive result for AATD. In a survey of patients with AATD, equal numbers of respondents reported negative and positive aspects of the diagnosis on their relationships and marriages.¹⁷ In asymptomatic adults no studies have been performed that have evaluated the psychologic effects of predispositional testing. In asymptomatic children neonatal screening programs have beneficial effects in terms of highlighting the need for smoking cessation among parents¹⁸ and reducing smoking rates among children. Childhood diagnosis of AATD has been associated with psychologic stress for parents, leading to problematic interpersonal relationships.²⁸ The children might not suffer additional psychologic burden, at least in early adulthood.²⁹

The identification of possible future illness in asymptomatic subjects also raises important ethical issues regarding confidentiality, privacy, and duty to disclose to employers and insurance providers.³ If patients do receive an early diagnosis of AATD, they might be able to anticipate any employment-related issues and manage insurance needs. There is limited evidence on the prevalence of discrimination by employers or insurance providers involving patients with AATD. One patient survey reports that 15.8% of patients with AATDs lost jobs and 10.5% lost health

FIG 1. ATS/ERS recommendations for AAT testing.³

insurance after a diagnosis of AATD, although the reasons why health insurance was lost were not reported.¹⁷ In the United States the Americans with Disability Act, the Equal Employment Opportunity Commission, and the Health Insurance Portability and Accountability Act provide protection against discrimination by employers or life and insurance providers. Based on the Health Insurance Portability and Accountability Act, an employer cannot base hiring or firing decisions on health-related information and cannot have the patient's medical information. Protection against discrimination on the basis of genetic information is about to be improved by the HR493 Genetic Information Non-discrimination Act, which has been passed in the House of Representatives (April 2007) and will be voted on in the Senate later in 2008. This legislation will prevent employers using a person's genetic information when making hiring, firing, job placement, or promotion decisions. HR493 will prevent health insurers from using genetic information to deny coverage or determine premiums.

The ATS/ERS guidelines recommend that physicians weigh the risks and burdens associated with an early diagnosis through screening and discuss them with the person being tested.³

TYPES OF DIAGNOSTIC TESTS

Diagnostic testing includes both quantitative tests for plasma AAT levels and qualitative blood tests for the identification of AAT genetic variants (Fig 1).³ Costs of each vary between expert centers.³⁰

Plasma AAT levels

Plasma AAT levels are usually measured quantitatively by means of rocket immunoelectrophoresis, radial immunodiffusion, or nephelometry (Fig 1).³ These tests are readily available, simple to order, and low cost. However, radial immunodiffusion overestimates AAT concentration by 35% to 40%.³¹ Nephelometry can overestimate AAT levels because of interference from

hemoglobin or lipids.³ Another consideration is that AAT is an acute-phase reactant, and inflammatory conditions can increase the steady-state plasma AAT concentration in Z heterozygotes.³ In particular, AAT levels are increased during exacerbations and should therefore not be measured during these events. A protective threshold has been observed in which AAT levels of greater than 11 μ M do not appear to be associated with an increased risk for emphysema. The threshold level differs depending on the detection method used and corresponds to 80 mg/dL if measured by means of radial immunodiffusion and 50 mg/dL if measured by using the standard method, nephelometry (Table II).³ A patient with an AAT level measured at 140 mg/dL during an exacerbation will require further investigation to confirm baseline levels.

AAT is an acute-phase protein. Levels of AAT can be relatively increased in patients with acute and chronic inflammatory conditions, infections, stress, and some cancers and are also increased in pregnant women and those taking oral contraceptives. The result might be false normal levels of AAT detected in patients with mild-to-moderate AATD.³ Therefore in patients with abnormal (<120 mg/dL) or borderline (90-140 mg/dL) AAT levels, phenotyping and genotyping is performed to confirm AATD (Fig 1). A combined approach of analyzing levels and searching for the most common deficient variants (Z and S) through commercially available test kits is a common approach to diagnosing AATD.

Phenotyping

Phenotyping is performed after a single quantitative AAT test shows abnormal or borderline levels (repeat testing of AAT levels over time is not common practice, Fig 1). Although the term is not used correctly in AATD, phenotyping refers to identifying AAT variants with isoelectric focusing (IEF), which separates the variant proteins based on their isoelectric point. Phenotyping can be performed on serum or plasma samples. The variant proteins are

TABLE II. Methods used to determine plasma AAT levels, the normal range for each method, and the protective threshold value³

Method	Normal range	Predictive threshold
Radial immunodiffusion	150/200-250/400 mg/dL*	80 mg/dL*
Nephelometry	83/120-200/220 mg/dL*	50 mg/dL, 11 μ mol/L†

*Value obtained from commercially available standards.

†Value obtained by using the National Heart, Lung, and Blood Institute standards.

named alphabetically from A to Z according to the distance they migrate through the electrophoretic gel, with rapidly migrating variants designated early letters in the alphabet and those migrating more slowly designated later letters. An illustration of an IEF gel showing common AAT variants appears in Fig 2. This technique requires specific expertise because interpretation of the gels is challenging due to the complex microheterogeneity of AAT and the large number of variants involved.³² In addition, there are no commercially available controls or reagent sets. It is recommended that an experienced reference laboratory performs the test.³ Despite these shortcomings, this technique remains an informative part of potential screening and diagnostic modalities.³³

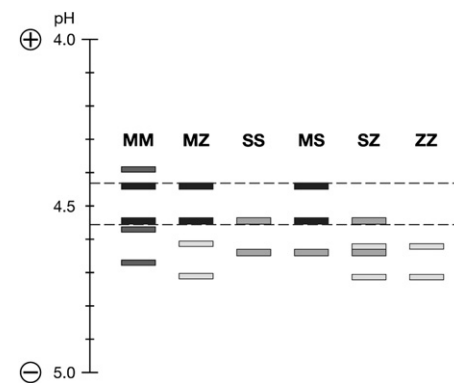
Fingerstick tests can be used to identify common phenotypes, can be administered at home, and have the potential advantage of avoiding venipuncture. Patients taking home tests receive support from a call center, as demonstrated in the Alpha Coded Testing Study.^{16,34} Genetic testing (genotyping) in this study successfully identified patients with MM, MZ, MS, SZ, ZZ, and PIZ-null phenotypes, as well as 12 other deficient alleles. Use of dried-blood spot samples enables easier transportation of samples. Identification of a deficient variant should be confirmed with serum or plasma samples.³

Genotyping

Diagnosis at a molecular level (genotyping) uses DNA extracted from circulating mononuclear blood cells. Allele-specific amplification or analysis allows known mutations to be identified (Fig 1). Test kits are available that can detect S and Z alleles in samples of whole blood or mouthwash samples, although they cannot detect rarer null alleles.³ If no known mutations are identified, direct sequencing or denaturing gradient gel electrophoresis is performed (Fig 1).

Optimal laboratory evaluation of AATD

The most appropriate laboratory methods for evaluating AATD are not well defined. How and when additional phenotyping and genotyping tests are performed and the method used is not standardized. A recent study suggested that genotyping should be used in combination with a measurement of serum AAT levels, with additional IEF phenotyping when genotyping and serum AAT level results are discordant.³⁵ Snyder et al³⁵ reported that use of a PCR-based assay system that identifies the Z and S alleles used in tandem with a measurement of serum or plasma AAT concentration accurately identifies approximately 96% of all patients with AATD when compared with IEF. Approximately 4% of all samples submitted for AATD genotyping required additional IEF phenotyping. In these cases the serum concentration of

**FIG 2.** Illustration of an IEF gel with common AAT variants.

AAT did not correlate with the determined genotype.³⁵ The strength of this approach is that genotyping is straightforward and provides unequivocal identification of the most common alleles associated with AATD. The addition of AAT concentration determination identifies those samples with rare deficiency alleles not recognized by genotyping for the S and Z alleles.³²

Additional tests

When AATD is confirmed, it is important to determine the severity of pulmonary impairment (Fig 1). Initial assessment should include a chest radiograph, a computed tomographic scan, spirometry, static lung volume measurement, arterial blood gas analysis, and gas transfer capacity. This will provide a full baseline assessment of the pulmonary physiologic status of the patient with AATD.³ Future progressive decrease in lung function can be measured from this established baseline. In addition, AATD testing should be offered to a patient's spouse and other family members (Fig 1).

Incorporating ATS/ERS guidelines for AATD testing into diagnostic protocols

Despite recommendations by the ATS/ERS for AATD testing in specific individuals (Fig 1), health care providers are not following these testing guidelines in clinical practice.³² The reasons for this are unclear, but in the United States they might include a lack of genetics training in residency programs and failure to incorporate the latest technologic advances, which make the molecular diagnosis of AATD less challenging.³² Increased awareness of AATD and the use of less-complex approaches to genetic testing for AATD will hopefully increase the frequency of AATD testing. The continuing educational and research efforts of organizations such as the Alpha One Foundation and industry-sponsored groups will be key to help achieve this goal.^{22,36} For instance, a recent surveillance study conducted by the Respiratory and Allergic Disease Foundation used a simplified testing program and found that 3.3% of adult patients with persistent asthma, COPD, or both had low AAT levels.²⁵ AATD testing was recommended for all patients with persistent asthma, COPD, or both with loss of lung function.²⁵

Treatment options specific for AATD

At its core, AATD is emphysema. Treatment should focus on noxious stimulant avoidance, bronchodilators, oxygen, pulmonary

rehabilitation, and proper nutrition. These are the same recommendations for patients with COPD that is not caused by AATD. Management of acute exacerbations in patients with AATD should also include inhaled steroids as used for AAT-replete patients with COPD.^{3,37}

Augmentation therapy

Replacement α_1 -proteinase inhibitor (A1-PI) therapy is recommended for patients with AATD with established airflow obstruction, regardless of phenotype.³ To date, several studies have evaluated the effects of augmentation therapy on the development of emphysema in patients with AATD and have shown that augmentation therapy is safe and effective in increasing serum A1-PI levels.³⁸⁻⁴³ In addition, one study reported improved survival in patients receiving augmentation therapy compared with control subjects, especially in patients with FEV₁ of 35% to 49% of predicted value.⁴²

Lung function testing is commonly used to assess the efficacy of augmentation therapy, and there is evidence from 3 studies suggesting a reduction in the rate of decrease of FEV₁ with augmentation therapy.^{40,42,43} Some studies have suggested that computed tomographic scanning to measure lung tissue density shows promise for providing a practical and quantitative way to assess the efficacy of augmentation therapy in the future.^{44,45} To date, there is not a simple reproducible method to establish the biochemical efficacy of dosing of augmentation therapy.

Lung transplantation

Lung transplantation has become an additional treatment option for many patients with end-stage lung disease. Approximately 8% of all lung transplantations worldwide are performed in patients with emphysema associated with AATD.⁴⁶ Posttransplantation augmentation therapy is not generally recommended for patients with AATD, except during episodes of acute rejection or infection and possibly during chronic rejection.³

Lung volume reduction surgery

Lung volume reduction surgery (LVRS) involves the resection of 20% to 30% of the most severely involved areas of emphysema with poor perfusion. However, it is unclear whether LVRS improves lung function in patients with emphysema associated with AATD because they were excluded from the National Emphysema Treatment Trial.⁴⁷ The existing guidelines do not regard LVRS as appropriate for these patients.³

SUMMARY

AATD is one of the most common potentially fatal genetic diseases in the white population. Affected individuals are at a high risk of emphysema or liver disease. Despite its prevalence, AATD is underrecognized and underdiagnosed. The ATS and ERS have developed guidelines to promote early diagnosis of AATD, giving patients the opportunity to make educated decisions about their lifestyle and to receive the recommended A1-PI augmentation therapy. Even with the stimulus of the guidelines, routine testing for AATD in high-risk patients is not the norm, and thus continuing publicity is required. In addition, further development of laboratory protocols is encouraged to define how and when additional phenotyping and genotyping tests should be performed.

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