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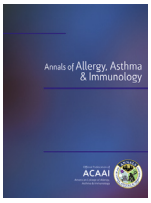

Distinguishing alpha$_1$-antitrypsin deficiency from asthma

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ABSTRACT

Objective: To explore the relations that exist between α_1-antitrypsin deficiency (AATD) and asthma and to evaluate practices for screening patients with asthma for this genetically determined condition in the context of current guidelines.

Data Sources: English-language articles were selected from a PubMed search using combinations of the following search terms: *alpha$_1$-antitrypsin*, *screening*, and *asthma*.

Study Selections: Studies to be included in this review were based on the authors' expert opinions.

Results: Asthma and AATD are 2 distinct conditions yet they can coexist. Although AATD has a variable symptomatology and some patients may be asymptomatic, many can present with symptoms that are similar to those of asthma, such as dyspnea, wheezing, cough, and mucus production, which can cause confusion at diagnosis. A simple genetic test exists for AATD, which is a single-gene disorder, and the American Thoracic Society and European Respiratory Society guidelines recommend the screening of patients with asthma who exhibit chronic airflow obstruction. Patients with AATD are seen by internal medicine, family medicine, allergy, and pulmonary clinicians, yet there is a generalized lack of awareness of testing among all specialties. This leads to a delayed diagnosis for patients with AATD, typically by 8.3 years.

Conclusion: A greater awareness of AATD among clinicians who regularly manage patients with asthma symptoms could increase diagnosis rates, thus optimizing interventions and management strategies to improve patient outcomes.

Introduction

Alpha$_1$-antitrypsin deficiency (AATD), an autosomally inherited disease resulting in low circulating levels of alpha$_1$-antitrypsin protein, leads to early-onset chronic obstructive pulmonary disease (COPD).[1] In some patients, extrapulmonary symptoms can occur, most notably liver disease.[2] The vast majority (>90%) of individuals with AATD remain unaware of their condition.[3] Underdiagnosis of AATD might stem from a misperception of low prevalence, misinformation about the usual presentation of a patient, and a misunderstanding that asthma and AATD are mutually exclusive disease entities. Although the etiology and disease mechanisms of asthma and AATD are distinct, patients with AATD commonly first present with asthma-like symptoms[4] and initially receive asthma treatment. Adding to the confusion, it has been recognized that allergy and asthma often coexist with AATD.[4] Owing to overlapping clinical features, AATD is often overlooked in the differential diagnosis of asthma and can be misdiagnosed as asthma.[1] Despite ongoing efforts to educate on the need for testing and international guidelines for whom should be tested, most patients who are candidates for screening, including those with chronic asthma, are not tested. It has been reported that, on average, patients with AATD endure a delay in diagnosis of approximately 8 years and must see multiple health providers before a simple blood test to make the diagnosis is ordered.[5]

The purpose of this review is to explore the interactions and overlap between AATD and asthma. The authors examine the clinical consequences of AATD and discuss the rationale for extending AATD screening to patients with asthma based on currently available evidence. If patients with symptoms of asthma are targeted for AATD screening, research suggests that the disease might be detected sooner and disease-specific interventions could be implemented.

Body

Pathophysiology of Respiratory Disease in AATD

Alpha$_1$-antitrypsin (AAT) is a 52-kDa glycoprotein isolated in the 1960s from the alpha$_1$-globulin fraction of blood that was demonstrated to inhibit trypsin.[6] As a member of the serine protease inhibitor (SERPIN) family of proteins, it inhibits different

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proteinases and also is known as alpha$_1$-antiproteinase. AAT is primarily produced and secreted by hepatocytes and is locally secreted by epithelial cells, alveolar macrophages, and neutrophils.[7–9] The protein circulates to the lungs through the bloodstream, where its principal activity is to protect the lungs from damage induced by the protease enzyme neutrophil elastase (NE). As part of the normal physiologic response to infection and inflammation, NE degrades components of the extracellular matrix in the clearance of damaged tissue[10] and may have other antibacterial[11] and proinflammatory[12] effects. In healthy individuals, AAT protects the alveoli from the proteolytic effects of NE by maintaining a balanced milieu between anti- and proinflammatory proteins in the lower respiratory tract.[13] It also inhibits other neutrophil proteases, such as protease-3 and cathepsin-G, and counteracts the cytotoxic effects of neutrophil defensins.[14]

There are several lines of evidence implicating AAT as a participant in the immune response.[15,16] In addition to NE, AAT is an acute-phase reactant.[3] Upregulation of AAT occurs in response to infection and tissue injury, to aid in tissue repair, in a mechanism that is mediated by interleukin-6 and tumor necrosis factor-α. AAT also inhibits various lymphocyte cytotoxic reactions, including T-cell, natural killer cell, and antibody-dependent cell-mediated processes. Moreover, AAT is thought to decrease the ability of natural killer cells to bind to their target cells.

In the case of AATD, inheritance of deficiency alleles,[6] such as proteinase inhibitors (Pi) Z, S,[1] or F,[17] or a "null" allele[1] causes decreased, severely deficient, or a complete absence of AAT in the serum, leading to a protease (ie, NE)/antiprotease imbalance.[13] Elastin and other extracellular matrix components in the lower respiratory tract and alveoli are degraded, resulting in emphysema[1] with progressive obstruction and lung function loss. In addition to enzymatic changes, the Z form of the AAT protein forms polymers in the lung that act as chemoattractants, thereby recruiting more neutrophils and amplifying tissue destruction.[18]

When the lung is regularly exposed to inflammatory stimuli, it is particularly vulnerable to excess NE activity.[19] Lung damage is greatly accelerated by smoking[20] and recurrent infections, such as chronic bronchitis and pneumonia, and is significantly affected by asthma, all of which contribute to unchecked inflammation and unopposed NE activity in the AATD state.

AATD: A Common Genetic Disease

Alpha$_1$-antitrypsin deficiency is one of the most common hereditary disorders in the world,[21] with a higher genetic prevalence than cystic fibrosis in whites.[1] The AAT gene (HUGO name Clade A1) spans 12 kb on the long arm of chromosome 14 in the SERPIN cluster of genes,[22] and it is the Pi locus that encodes the AAT protein. Pi alleles are inherited codominantly, with genes from both parents contributing to the overall AAT level. More than 100 AAT alleles are known to exist, and approximately 35 of these alleles result in decreased or absent plasma AAT.[23] Population-based screening studies have confirmed the high prevalence of AATD alleles,[24,25] although most of these variants are rare.

The common AAT alleles are M, S, and Z, which correlate with the expressed proteins' phenotypes and their migration speed on an electrophoresis gel (M, medium; S, slow; Z, very slow). M is the most common allele, present in 80% of individuals, and encodes a normal AAT protein.[26] The S and Z alleles result in abnormal protein with abnormalities in structure and function. In AATD, protein expression is typically lower than 30% of the normal concentration. In patients with the PiZZ genotype, which leads to severe disease, protein expression is in the order of 10% to 15% of that found in patients with the PiMM genotype.[1]

Clinical AATD is most commonly caused by the homozygous inheritance of the Z allele, which is created by an amino acid substitution from glutamic acid to lysine at position 342 in the fifth exon. This amino acid change occurs in the hinge region of the reactive site loop, which disrupts a salt bridge that stabilizes the hinge region and the major beta sheet.[27] This disruption of the β sheet allows for the intercalation of a reactive site loop of another Z-AAT molecule into its opened β sheet, creating the formation of Z-AAT polymers. The polymerization of abnormal AAT proteins is thought to be largely responsible for the substantial decrease in AAT secretion from hepatocytes, owing to its retention in the endoplasmic reticulum, and more rapid destruction of the protein.[28,29]

The postulated protective threshold of serum AAT is 11 μmol/L.[1] In patients with the PiSZ and PiZZ phenotypes, the AAT concentrations average 8 to 16 μmol/L and 2.5 to 7 μmol/L, respectively,[1] and the extent of the deficiency is accompanied by a corresponding degree of emphysema. As expected, computed tomograms have shown a much higher frequency of emphysema in patients with the PiZZ phenotype than with the PiSZ phenotype.[30] More than 1 million individuals across the globe are thought to have the PiSZ phenotype, and it is estimated that approximately 180,000 have the severe deficiency phenotype, PiZZ.[31]

Dilemmas in AATD Diagnosis and Overlap with Asthma

Although AATD is one of the most prevalent diseases that can lead to significant morbidity and mortality, AATD continues to be underdiagnosed in patients presenting with airflow obstruction. Under-recognition of the disease is due in part to misconceptions about the profile of a "typical" patient with AATD. The usual description of a patient with AATD as a young person with an unremarkable smoking history who has end-stage emphysema is actually an uncommon presentation. In a study that conducted universal testing of 965 patients with airway obstruction, the average age of those with the PiZZ genotype was 55.9 $\pm$ 9.8 years.[32] In another study, the average smoking history of those with ZZ at the time of diagnosis was 23.2 $\pm$ 14.5 pack-years.[33]

Current international guidelines recommend AATD screening in all patients with obstructive lung disease, including the Global Initiative for Chronic Obstructive Lung Disease[34] and the World Health Organization.[35] The consensus statement on AATD by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) specifically recommends genetic screening in all symptomatic adults with emphysema, in patients with asthma who have airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators, and in all individuals with unexplained liver disease[1] (Box 1).

With respect to asthma, there is an absence of any systematic recommendation for AATD screening in current guidelines on the prevention and management of asthma,[36,37] thus contributing to lack of recognition of AATD in patients with asthma. Patients with AATD often have symptoms that overlap those in all obstructive lung diseases, especially asthma. Coupled with the variable symptomatology that can be seen among different patients with AATD, diagnosing AATD in the context of asthma can be confusing. Although some patients are asymptomatic, many present with asthma-like symptoms,[38] including dyspnea (84%), wheezing (65%), cough without upper respiratory tract infection (42%), and cough with mucus production (50%).[39] Not surprisingly, AATD is most commonly misdiagnosed as asthma,[40] contributing to a considerable delay in the correct diagnosis. To complicate matters, AATD is frequently seen in patients with asthma and, conversely, patients with AATD are susceptible to developing asthma owing to increased underlying lung inflammation,[41] leading asthma to coexist with AATD and emphysema. In a study of patients with poorly controlled asthma, AATD was present in 2% to 3% of subjects, with 10.5% being carriers of a deficiency gene.[42]

Box 1. ATS/ERS Task Force Recommendations on Which Individuals Should Undergo Diagnostic Testing for AATD (Type A Categorization) and for Whom Discussion of Testing Is Appropriate (Type B Categorization)[1]

Type A: Recommendation for Testing

- All adults with symptomatic emphysema, regardless of smoking history
- All adults with symptomatic COPD, regardless of smoking history
- All adults with symptomatic asthma whose airflow obstruction is incompletely reversible after bronchodilator therapy
- Asymptomatic patients with persistent obstruction on pulmonary function tests with identifiable risk factors (ie, cigarette smoking, occupational exposure)
- Siblings of individuals with AATD
- Individuals with unexplained liver disease and adults with necrotizing panniculitis

Type B: Discussion of Testing

- Adults with bronchiectasis without evidence of etiology
- Adolescents with persistent airflow obstruction
- Asymptomatic individuals with persistent airflow obstruction and no risk factors
- Adults with positivity for cytoplasmic antineutrophil cytoplasmic antibodies (antiproteinase-3) vasculitis
- Individuals with a family history of COPD or liver disease not known to be attributed to AATD
- Immediate or distant relatives of an individual homozygous for AATD

In 1963, Laurell and Eriksson[6] first reported on individuals with AATD who had clinical symptoms suggestive of bronchial asthma and demonstrated the presence of emphysema. In the National Heart, Lung, and Blood Institute's Registry of AAT Deficient Individuals, which reported the baseline characteristics of more than 1,000 patients, 55% of patients had a significant response to a bronchodilator.[43] In addition, 31% of patients carried a diagnosis of asthma and 23% had allergies affecting the respiratory tract.[39] The lung pathology of patients who died during the National Heart, Lung, and Blood Institute registry presented with airway disease in the small and large airways characterized by goblet hyperplasia and mild inflammatory processes.[44,45]

An association between AATD and liver complications came several years after the first description of the disease.[2] In children, 10% to 15% of those with the PiZZ genotype develop symptoms of liver disease,[46] with protracted jaundice and elevated liver enzymes being the most frequent symptoms in infants.[1] In adults, liver cirrhosis is seen less frequently than the pulmonary symptoms of AATD and mainly in men older than 50 years.[20] Another uncommon extrapulmonary symptom of AATD is necrotizing panniculitis, an inflammatory condition of the skin and subcutaneous tissue.[1] Although COPD and emphysema are the primary symptoms of AATD, these other features constitute an important distinction from asthma.

In most individuals with severe AATD, asthma is diagnosed after COPD symptoms have developed. It has been estimated that physician-diagnosed asthma is present in up to 50% of patients with AATD, once the symptoms of COPD have developed.[4] Asthma also can occur alone before COPD is diagnosed.[40] Whether asthma precedes or results from AATD, the presence of coexisting asthma significantly affects the course of AATD, because it is associated with more severe lung disease.[47] The prognosis for individuals who have asthma and AATD is poor.[47] There is evidence that patients with AATD who have bronchial hyper-reactivity have poorer outcomes and a more rapid decrease in lung function,[44,48] with steeper rates of decreased forced expiratory volume in 1 second (FEV_1) compared with subjects who had no hyper-reactivity (64.6 vs 40.2 mL/year).[43] When asthma coexists with AATD, it exacerbates COPD symptoms and is a risk factor for more severe COPD.[47]

The therapeutic options and outcomes differ significantly between asthma and AATD, which underscores the importance of making the correct diagnosis. Distinguishing AATD from asthma based on presentation and clinical evaluation is not possible. Baseline pulmonary function tests and asthma scores have been shown to be no different in patients with poorly controlled asthma with and without AATD.[42] Although a family history of liver and lung disease may lend support to its presence, diagnosis of AATD relies exclusively on laboratory assays.[49]

Comparisons between AATD and Asthma

An estimated 24 million people in the United States (approximately 1 in 12) have asthma (http://www.aaaai.org/about-the-aaaai/newsroom/asthma-statistics.aspx). Diagnosis is based on the thoughtful consideration of multiple variables, which may include presentation of classic symptoms, confirmation of allergy, demonstration of airway obstruction by spirometry and airway reactivity using bronchodilators, establishment of airway inflammation, and degree of responsiveness to anti-inflammatory treatments, such as corticosteroids.[36,37] In distinguishing AATD from asthma, the clinician must assess each of the elements in the context of the whole patient, particularly one who does not adhere to a typical clinical profile or course or who has recalcitrant disease.

Table 1
Key features of asthma and AATD

	Asthma	AATD
Prevalence[a]	24.6 million[b]	45,000–250,000[50]
Onset	variable	40–53 y[19]
Frequency	childhood > adulthood	adulthood > childhood
Family history	atopic disease (allergic rhinitis, eczema, asthma, food allergies)	asthma, emphysema, cirrhosis, and other liver disease
Special features	obstruction on spirometry is fully reversible	obstruction on spirometry is not reversible
Concomitant allergies	70%	22%[40]
Diagnosis	physical examination, PFTs, demonstration of reversibility	genetic testing, confirmation by phenotype testing
Treatment	glucocorticosteroids, leukotriene modifiers, β_2 agonists, anti-IgE[36]	as for COPD + AAT augmentation therapy

Abbreviations: AAT, alpha$_1$-antitrypsin; AATD, alpha$_1$-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; IgE, immunoglobulin E; PFT, pulmonary function test.
[a]Estimated prevalence in the United States.
[b]http://www.aaaai.org/about-the-aaaai/newsroom/asthma-statistics.aspx.

Box 2. Common Strategies for Diagnosing AATD[3]

- AAT level—serum testing that reports the circulating AAT concentration
  - May be increased by illness or inflammation
- AAT phenotype
  - Performed by isoelectric focusing on electrophoresis gel
    - A low α-globulin fraction on serum protein electrophoresis, performed for other reasons in a patient with pulmonary problems, may indicate the need to screen for AATD
  - Differentiates the different α1 proteins produced compared with known variants
    - This method cannot detect "null" alleles, because in these cases no AAT protein is produced
- AAT genotype—performed by polymerase chain reaction; detects common proteinase inhibitor gene alleles (M, S, Z); may determine affected individuals and carriers of disease regardless of AAT level; and can form the basis of initiating genetic counselling

Regardless of overlapping clinical characteristics, any patient with difficult-to-manage asthma should be screened for AATD. The key features of asthma and AATD are presented in Table 1.[19,36,40,50] Considerations for diagnosis are reviewed below.

Age of Presentation

Although asthma is a heterogeneous disease that may present at any age, it often becomes apparent during childhood and occurs more frequently in youth. In contrast, the clinical manifestations of AATD are rarely seen before 25 years of age and more often occur as hepatic illness when presenting in childhood.[1]

Personal or Family History and Evidence for Atopy

Given that the majority of asthma (60%–80%) is allergic by definition, ie, caused by IgE-mediated airway inflammation and hyperresponsiveness to allergens,[51] there is usually evidence toward genetic predisposition or the presence of other allergic phenomena. The National Heart, Lung, and Blood Institute's expert panel guidelines recommend allergy testing in the diagnosis and management of persistent asthma.[36] Within the workflow of managing the adult patient with asthma, the absence of allergy should prompt the physician to consider AATD in the differential diagnosis.

Smoking History

In the case of a patient with asthma who smokes, the concomitant use of cigarettes may exacerbate pulmonary symptoms and obscure the fact that another underlying disease exists. Symptom onset after a relatively short period of tobacco use or a lack of improvement in symptoms after smoking cessation should lead the physician to consider screening for AATD.[33] Active tobacco use should not lead the physician to overlook a possible diagnosis of AATD. Ideally, active and passive tobacco exposure should always provoke screening for AATD because smokers are a high-risk population with poorer outcomes. Furthermore, screening can be a tool with which to educate patients and effect behavior change.[52]

Physical Examination

Distinguishing a patient with AATD based on physical examination alone is not possible.[49] Patients with severe obstructive lung diseases can appear completely normal at a physical examination. Findings from the examination that are discordant with the patient's history might lend a clue to expanding the differential diagnosis. Certainly, any patient with asthma who has features that are suggestive of chronic air trapping should be a candidate for AATD screening.

Spirometry and Other Diagnostic Tests

Spirometry should always be included in the evaluation of asthma, including responsiveness to bronchodilators. Lack of any or complete reversibility to normal values after bronchodilation may indicate components of fixed or irreversible obstructive lung disease, which should trigger the clinician to think about AATD. This may include patients with a decreased FEV_1 of less than 80%, a ratio of FEV_1 to forced vital capacity no higher than 0.7, or even patients who have a normal FEV_1 or a normal ratio of FEV_1 to forced vital capacity but an abnormal forced expiratory flow rate of 25% to 75% that does not improve after bronchodilator administration.[53,54] In the annual evaluation of the patient with asthma, progressive decreases in lung function are also atypical and should incite the clinician to screen for AATD. Other considerations may include pulmonary function testing that shows increased total lung capacity and residual volumes, normal exhaled nitric oxide levels in the setting of active asthma symptoms, a predominance of neutrophils rather than eosinophils from bronchial washings or biopsies, negative methacholine or mannitol challenge results, and/or evidence of hyperinflation on chest radiographs or computed tomograms.

As mentioned earlier, a secondary complication of AATD can be liver disease.[2,36] In a patient with presumed asthma and a medical history of elevated liver enzymes or a family history of liver cirrhosis, it would be prudent to consider testing for AATD.

Resistance to Usual Asthma Treatment

When the patient with asthma shows a lack of improvement after receiving the usual therapeutic interventions, there can be several factors involved, including problems with adherence to the medication regimen, environmental avoidance measures, and comorbid disease. Any difficult-to-manage asthma case should be considered for AATD screening. These may be cases of recurrent exacerbations, a chronic bronchitis picture, steroid dependence, and "brittle" asthma. In patients with recalcitrant asthma, medication nonadherence, comorbid disease, and AATD are more common than corticosteroid resistance, although corticosteroid insensitivity is more frequently contemplated.[36]

Discussion

AATD Screening

When approaching atypical or challenging asthma cases, the acute clinician will consider whether AATD is present or coexistent. The recommendations of the ATS/ERS Task Force for AATD provide guidance on the differential diagnosis and screening of AATD.[1] The only way to screen is by blood tests, as summarized in Box 2.

The AATD testing involves the collection of a few drops of blood onto a filter paper. Then, the dried blood is sent to a specialized laboratory that performs a polymerase chain reaction test to detect the most common AATD alleles (M, S, or Z). If a positive result is returned using this method, further tests are initiated to determine the patient's AAT serum level and phenotype (by gel electrophoresis). The full panel of diagnostic tests for AATD involves serum level quantification, phenotyping, and genotyping. For high-throughput screening, polymerase chain reaction–based methods are available, whereas DNA sequencing can be used to define specific genotypes, including rare alleles.

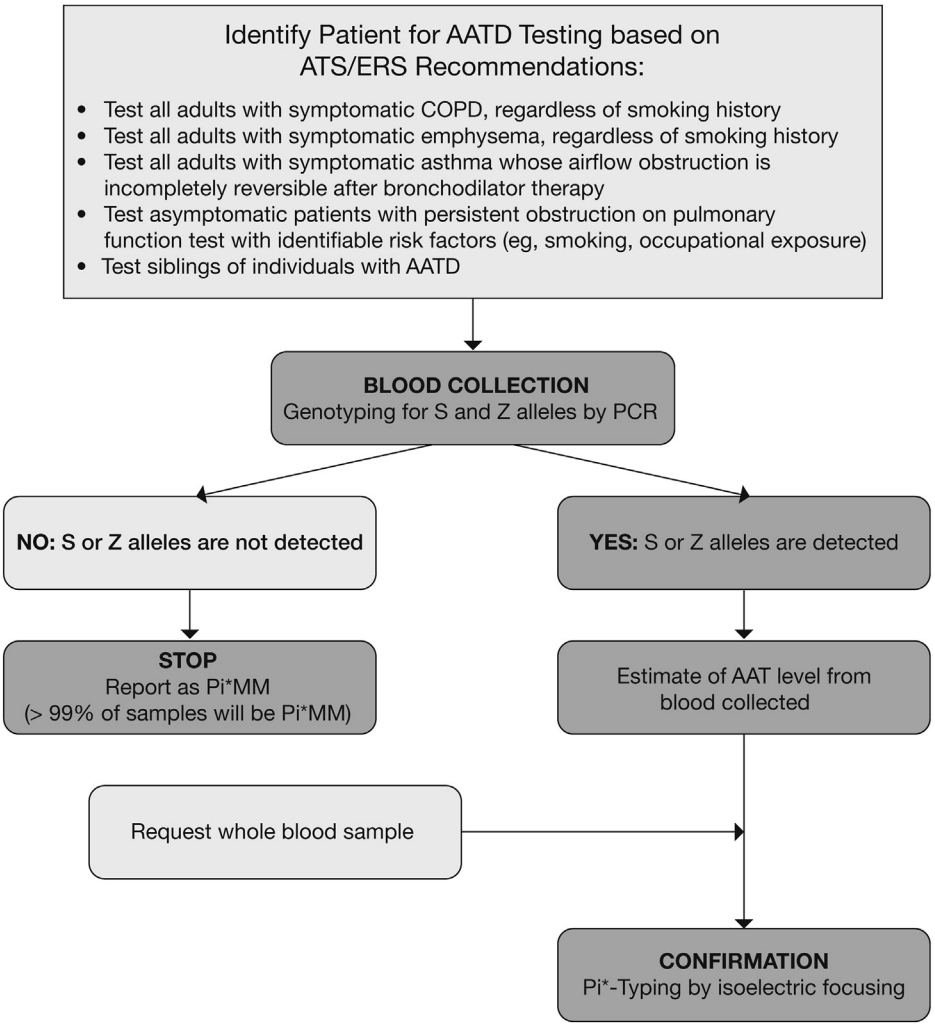

Figure 1. Example of an AATD testing algorithm. With this scheme, rare allele variants will not be picked up and further investigation may need to be considered if clinical suspicion of AATD is high. AAT, alpha$_1$-antitrypsin; AATD, alpha$_1$-antitrypsin deficiency; ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; PCR, polymerase chain reaction; Pi, proteinase inhibitor.

A spectrum of disease exists for AATD and low to normal serum levels might provide false reassurance. Testing for AAT levels alone in a patient with pulmonary problems who has frequent lung exacerbations or infections may result in cases of mild to moderate AATD being overlooked and for carriers of 1 deficiency-related allele (eg, PiMZ) to be missed. A further limitation of serum testing alone is that AAT can be elevated when infection, cancer, thyroid disorders, and other forms of inflammation are present and may be increased by oral contraceptives, pregnancy, and stress.[55] Genetic testing, coupled with confirmation of the patient's phenotype, is the optimal method of diagnosing AATD.[56]

Screening patients with COPD for AATD has greater impact than population screening because it shows a much higher prevalence of AATD genotypes.[57] Targeted screening of patients with asthma may expose a similar situation. Screening rates might be improved further by involving the wider multidisciplinary team, ie, respiratory therapists and pulmonary function technicians, in testing candidate patients for AATD.[58] The participation of allergists or immunologists, in addition to that of other physicians who evaluate and manage pulmonary conditions, is an important facet of identifying patients with AATD. By introducing a testing algorithm into their clinic's work stream, such as that shown in Figure 1, it could be possible to systematically test all patients whose symptoms are highly suggestive of AATD.

Importance of Early AATD Identification

The average age of diagnosis for AATD is 45.5 ± 9.5 years, with 30% of patients diagnosed after 50 years of age.[5] Directed AATD testing in patients with moderate and severe asthma may result in the detection of not only more patients but also of younger patients. Early diagnosis of AATD enables patients and their families to make lifestyle changes to lower the risk of emphysema, decrease infection rates, and optimize their long-term clinical outlook.

The most important preventable risk factor for the progression of lung disease in AATD is cigarette smoking, which is often associated with a lower FEV_1 and earlier development of COPD.[47] Prognosis is poor for patients with the PiZZ phenotype who smoke because they have significantly lower survival rates than their nonsmoking counterparts and are expected to die up to 20 years sooner.[20] Smoking cessation should be persistently advocated to slow the progression of lung disease. In a study of smokers, patients who were diagnosed with AATD were more likely to attempt smoking cessation than their counterparts who did not have AATD.[52] Patients who are aware of their diagnosis and the risk factors for progressive disease are more willing and are more successful in quitting smoking.

Patient reluctance to test for AATD can pose a possible barrier. Studies of other genetic diseases have indicated that patients

Box 3. Take-Home Points

- AATD is highly under-recognized
- A high index of suspicion is needed so that screening for AATD takes place
- Patients with AATD often present with coexisting asthma and/or asthma-like symptoms
- Patients with asthma who have moderate to severe disease, unusual features, frequent exacerbations, features of fixed obstruction on spirometry, or are difficult to manage should be screened for AATD
- AATD can be confirmed only by blood testing, which is rapid and accessible
- Education and testing for AATD is a tool to prompt smokers to quit their tobacco habit
- Treatment with AAT augmentation therapy in deficient patients is available and may reduce further decreases in lung function
- Early identification leads to early intervention, education, and treatment
- Targeted screening of patients with asthma and COPD will increase identification of patients with AATD, allow faster diagnosis, and assist in identifying and preventing disease in family members

When to Consider Screening of Patients with Asthma

- Strong family history of emphysema, death from a respiratory disease, or cirrhosis
- Asthma without evidence of atopy (negative skin and/or blood test result)
- Asthma that has features of chronic bronchitis or emphysema by subjective or objective measurements
- Asthma that does not improve with usual therapy, or "brittle" asthma
- Steroid-dependent asthma or asthma that is unresponsive to steroids

exhibit anxiety toward undertaking genetic tests[1] and have negative attitudes toward the perceived outlook for their future health and that of their family members.[59] In eliciting participation in screening, patients should be informed that genetic testing is important for eliminating or confirming a diagnosis of AATD and that an earlier diagnosis translates to earlier initiation of management strategies, which can lead to improved outcomes, not only for themselves but also for afflicted family members. Diagnosis of a genetic disorder can have a significant psychologic impact on patients by giving them a reason for their symptoms, leading to effective behavioral changes.[1,52] Improved awareness of AATD and its complications, knowledge of an existing a support network or counseling, and availability of replacement therapy might reassure patients and encourage them to be evaluated.

Patients who are diagnosed with AATD and who have coexisting lung problems, such as recurrent or chronic infections, should continue to be aggressively managed, and full allergy testing should be given to those who have wheezing and asthma symptoms. Treatments aimed at decreasing bronchial hyper-responsiveness and inflammation may prevent further deterioration in FEV_1.[40] Vaccination against pneumococci and influenza significantly lowers exacerbation frequency in patients with AATD.[60] Moreover, yearly assessments of lung function, pulmonary rehabilitation, screening for hepatic disease, improving nutrition, and the use of supplemental oxygen are important management tools.[56] Although adjunctive treatments can temper inflammation and offer some degree of symptomatic relief, they do not address the underlying genetically determined deficiency, which is met by augmentation therapy with intravenous infusions of exogenous AAT. Clinical evidence has indicated positive effects on lung physiology with augmentation therapy,[43,50,61] which can stabilize lung function and slow down further lung destruction.[1]

Conclusion

$Alpha_1$-antitrypsin deficiency is a serious condition with a high prevalence among other genetic diseases. Although diagnostic testing is available, this is carried out infrequently during asthma consultations, even in patients who have symptoms that are highly suggestive of AATD. Raising awareness of AATD could be achieved by a change in the clinical practice guidelines that relate to diagnosing and managing asthma. Moreover, the availability of epidemiologic data on the coexistence of asthma and AATD could raise the profile of this genetic condition among immunologists who then might consider it as a differential diagnosis in their patients. The ATS/ERS recommendations inform the practitioner of the importance of distinguishing the "problem" patient with asthma, considering the differential diagnosis, and offering testing for AATD, and additional guidance is detailed in the take-home points that are listed in Box 3. Allergists or immunologists, primary care physicians, and other respiratory professionals are ideally situated to apply existing guidelines for AATD screening in obstructive lung disease to their patients with asthma. As a consequence, increased detection rates, earlier identification of the disease, and improved initiation of disease management strategies can occur, thereby making a positive impact on the long-term outcomes for patients and their families.

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