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Editorial

Might your respiratory patient have alpha-1 antitrypsin deficiency?

As the journal that focuses on the care of patients with chronic pulmonary disorders we want to enlist *Heart & Lung* readers in addressing an important problem.

In the primary care setting, it is important to screen adult patients with asthma and COPD for alpha-1 antitrypsin deficiency (AATD)

AATD is one of the most common hereditary diseases in the world, with a higher prevalence than cystic fibrosis. However, AATD is underdiagnosed and under-recognized,[1,2] partly as a result of misconceptions about the profile of a 'typical' AATD patient. AATD has no unique symptoms so clinicians don't often look to see if AATD might be the underlying cause for the chronic obstructive pulmonary disease (COPD) or asthma symptoms their patients experience. Without appropriate treatment, AATD can have a poor prognosis due to the ongoing accelerated deterioration of lung tissue, leading to lung transplantation or death. The time between the onset of respiratory symptoms and diagnosis of AATD has been estimated at 7.2 years for individuals with severe deficiency, with individuals having multiple primary care and specialist visits before obtaining the correct diagnosis.[3] Therefore, there is an urgent need for both early and accurate diagnosis of AATD so appropriate management can be put in place to slow disease progression and limit irreversible lung damage.

AATD is a monogenic hereditary disorder that increases the risk of lung and liver disease

Patients with AATD carry mutation(s) in the *SERPINA1* gene, leading to low levels or decreased function of the proteinase inhibitor alpha-1 antitrypsin (also known as, alpha-1 proteinase inhibitor, A_1-PI). The most common alleles include M (normal allele), Z (associated with severe AATD), and S (associated with mild AATD). In healthy individuals, the liver produces A_1-PI at levels required to protect lungs and other tissues from the activity of neutrophil elastase (NE). NE is a serine proteinase that plays a major role in various aspects of inflammation and when left unchecked, degrades elastin in connective tissues.[4] In people with AATD, NE can degrade healthy lung tissue, resulting in COPD and asthma-like symptoms.[5] Other clinical manifestations associated with AATD include diseases of the liver, skin, and vasculature.[6]

Triggers for testing include the diagnosis of COPD, abnormal spirometry, family history of lung or liver disease, or asthma in an adult that is only partially responsive to medical therapy

AATD may be suspected through either abnormal spirometry test results suggesting irreversible airway obstruction, or through known family medical history. The American Thoracic Society (ATS)/European Respiratory Society (ERS) statement recommends testing be carried out in individuals with emphysema, COPD or asthma with incompletely reversible airflow obstruction, and individuals with 'evidence of lung disease and smoking or occupational exposure'.[6] Similarly, individuals with a late onset of asthma-like symptoms should be tested (Table 1).[6–8] When AATD is suspected, an inexpensive blood test can assess A_1-PI serum levels to quickly lead to a diagnosis. The ATS/ERS statement also recommends genetic screening in a number of patient groups, including adults with symptomatic emphysema and/or COPD and siblings of individuals with diagnosed AATD.[6] Testing should not be seen as a financial burden; the Alpha-1 Foundation provides a free confidential testing program[9] and A_1-PI manufacturers also offer free AATD testing kits. AlphaNet, a not-for-profit peer- and self-management organization, provides a free disease management program for individuals with AATD.[10] Manufacturers support this program which is available to all individuals diagnosed with AATD. In addition, patient registries provide resources to patients (discussion forums, support groups) and actively contribute to the development of programs aimed at improving diagnosis and referral of AATD patients.[11,12]

A_1-PI augmentation therapy is the only treatment targeting the underlying cause of AATD-related emphysema

Administered intravenously at a weekly dose of 60 mg/kg body weight, augmentation therapy raises serum A_1-PI levels above the threshold thought to be the minimum level that protects against the risk of developing emphysema.[13] The clinical efficacy of A_1-PI augmentation therapy for AATD was suggested in two small randomized clinical trials and recently confirmed in the largest placebo-controlled randomized clinical trial (RAPID, NCT00261833) completed to date.[14–16] The RAPID trial was followed by the RAPID Extension trial (NCT00670007) in which eligible patients, including those who had received placebo in RAPID, received A_1-PI augmentation therapy for two years.

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Table 1
Characteristics of AATD and how to suspect, test and manage AATD individuals.[6–8]

Characteristics	• Monogenic hereditary disorder • Decreased levels or function of A_1-PI • Irreversible and progressive lung damage • Can lead to emphysema and/or bronchiectasis
Common symptoms	• Onset of symptoms in adults of any age • Dyspnea on exertion, cough, wheezing, chronic bronchitis, exacerbations
Suspecting AATD	• Emphysema diagnosis • COPD diagnosis • Asthma diagnosis with incompletely reversible airway obstruction and/or in individuals with late onset of asthma-like symptoms • Individuals with evidence of lung disease and smoking or occupational exposure • Unexplained liver disease • Necrotizing panniculitis • Siblings of individuals with diagnosed AATD
Testing	• A_1-PI blood levels • Pi-typing (protein phenotyping) • Genotyping
Disease management	• Lifestyle modifications • Pharmacological management of asthma and COPD-like symptoms • Usual management of liver disease • A_1-PI augmentation therapy in those with lung disease

A_1-PI, alpha-1 proteinase inhibitor; AATD, alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease.

An interim analysis showed a similar reduction in lung tissue destruction in all patients during the RAPID Extension trial, irrespective of the treatment received in the RAPID trial. In those patients who had received placebo during the RAPID trial, the lung density lost during the initial two-year period was not regained.[16] This finding demonstrates the disease-modifying effect of A_1-PI augmentation therapy in AATD patients and emphasizes the advantages of early diagnosis and treatment.

Targeted screening can enable early and appropriate intervention, and improve long-term outcomes

AATD symptoms can be managed via the implementation of lifestyle modifications such as smoking cessation, avoidance of environmental risk factors, and pulmonary rehabilitation. In addition, medications indicated in the treatment of COPD/asthma (e.g., bronchodilators, corticosteroids, antibiotics, supplemental oxygen) can also be given to alleviate respiratory symptoms. Early diagnosis facilitates discussion and prompt implementation of treatment options that will slow further deterioration and improve long-term outcomes.[6,16]

Nurses are ideally placed to raise awareness of AATD diagnosis and testing, and the availability of A_1-PI augmentation therapy

With the demonstrated efficacy and safety of A_1-PI augmentation therapy and the importance of lifestyle modifications in the management of AATD-related emphysema, it is fundamentally important to identify as early as possible individuals with AATD. Diagnosis rates and times need to be improved as early intervention is necessary to minimize disease progression and the irreversible loss of lung tissue. The implementation of screening algorithms in the primary care setting is therefore warranted to identify when asthma and COPD symptoms are due to AATD, and to identify patients who may benefit from treatment.

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