Ann Allergy Asthma Immunol 111 (2013) 458–464

Contents lists available at ScienceDirect

Distinguishing alpha$_1$-antitrypsin deficiency from asthma

Dareen Siri, MD [*]; Humam Farah, MD [†]; and D. Kyle Hogarth, MD [‡]

[*] Springfield Clinic LLP, Springfield, Illinois
[†] Hannibal Clinic, Hannibal, Missouri
[‡] University of Chicago, Chicago, Illinois

ARTICLE INFO

Article history:
Received for publication June 27, 2013.
Received in revised form August 28, 2013.
Accepted for publication September 23, 2013.

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

Reprints: Dareen Siri, MD, Springfield Clinic LLP, 1025 S 6th Street, PO Box 19248, Springfield, IL 62793-9248; E-mail: dsiri@springfieldclinic.com.
Disclosures: Dr Hogarth received remuneration from Grifols, Baxter, and CSL.
Funding Sources: Support for the development of this work was provided by Grifols Inc.

1081-1206/13
http://dx.doi.org/10.1016/j.anai.2013.09.019

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]