Original Article

The Allergist's Role in Detection of Severe Alpha-1 Antitrypsin Deficiency

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What is already known about this topic? Alpha-1 antitrypsin deficiency is underdiagnosed, with many patients experiencing years of symptoms and seeing numerous health care providers before appropriate diagnosis. Frequently, the first symptoms are dyspnea on exercise and can mimic asthma.

What does this article add to our knowledge? A survey of severe phenotype (ZZ, SZ, Znull, FZ) alpha-1 antitrypsin deficiency patients was conducted to describe their experience with allergist/immunologists in the diagnosis and treatment of their condition. We found that a third of study subjects were evaluated by allergy immunology but were only rarely diagnosed.

How does this study impact current management guidelines? Allergist/immunologists should increase screening of alpha-1 antitrypsin deficiency in patients with asthma who have fixed obstructive disease and patients with chronic obstructive pulmonary disease.

BACKGROUND: Alpha-1 antitrypsin deficiency (AATD) frequently presents as difficult to manage asthma or asthma with fixed obstruction and is well documented as being underdiagnosed in the population.
OBJECTIVE: This study aimed to better describe allergists'/immunologists' involvement in the care of patients with AATD and whether they currently contribute to the underdiagnosis by lack of screening for the condition.
METHODS: Using the Research Electronic Data Capture tool, we submitted a questionnaire to 500 patients with severe AATD (ZZ, SZ, ZNull, and FZ) through the Alpha-1 Foundation Research Registry to collect information about patient diagnosis and treatment patterns. Approximately 45% completed the questionnaire, leading to a final enrollment of 226 participants.
RESULTS: Seventy-eight participants (34%) had seen an allergist, but only 11 (5%) were diagnosed with AATD by their allergist. Likewise, allergists prescribed alpha-1 augmentation therapy to only 5 (8%) of the 59 patients on augmentation therapy. Nearly 46% (n = 104) of all participants were diagnosed with either asthma (28%) or allergic disease (18%) before receiving a diagnosis of AATD. Eighteen patients had been treated with immunotherapy before their diagnosis of AATD, with 94% of these participants receiving treatment for 3 years or longer.
CONCLUSIONS: Our data suggest that specialists in Allergy and Immunology should consider and screen for AATD in patients with asthma in whom spirometry does not return to normal. Furthermore, we propose allergists/immunologists are well suited to screen and treat patients with AATD. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Alpha-1 antitrypsin deficiency; Asthma; COPD; Emphysema; Screening for AATD; Diagnosis of AATD; Allergists*

Alpha-1 antitrypsin deficiency (AATD) is an autosomal-codominant condition that leads to decreased circulating levels of the glycoprotein alpha-1 antitrypsin due to either a homozygous or heterozygous mutation on the *SERPINA1* gene on the

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Abbreviations used
AATD- Alpha-1 antitrypsin deficiency
COPD- Chronic obstructive pulmonary disease
IT- Immunotherapy

long arm of chromosome 14.[1,2] In a minority of cases, patients may have dysfunctional alpha-1 antitrypsin protein despite normal serum levels, leading to similar consequences. At normal levels and function, alpha-1 antitrypsin inhibits neutrophil elastase from excessive proteolytic cleavage of elastin, a major extracellular protein important for tissue elasticity and a major component of lung tissue. As a result, individuals with AATD are at an increased risk to develop chronic respiratory symptoms from cumulative deterioration of lung tissue secondary to uninhibited neutrophil elastase during times of inflammation such as infection or environmental insults, namely, smoking.

Despite being commonly labeled as a rare disease, AATD is one of the most common autosomal genetic disorders and is considered highly underrecognized.[3] An estimated 100,000 individuals in the United States are believed to have the disorder, with greater than 90% of cases not diagnosed.[4] Although the condition is most prevalent in individuals with descendants from Western Europe, increasing evidence suggests that it presents worldwide.[5] The average delay in diagnosis is 5 to 7 years from the onset of symptoms.[6-10] Likewise, patients frequently see several health care providers before receiving the correct diagnosis.[10,11] The delay in diagnosis is attributed to significant overlap in symptoms of AATD with asthma and chronic obstructive pulmonary disease (COPD). The clinical manifestations of breathlessness, cough, phlegm production, wheezing, and fatigue can be indistinguishable between the disorders. However, AATD typically presents earlier in life during the third or fourth decade.[12] Furthermore, AATD can coincide with asthma, and patients with both AATD and asthma are more susceptible to developing progressive and accelerated lung loss because of constant unchecked inflammation.[13]

To improve quality of life and reduce morbidity and mortality in individuals with AATD, it is imperative that physicians work toward more prompt diagnosis and early initiation of treatment if indicated.[14] Our study explores the role of the allergist/immunologist in the diagnosis and treatment of patients with severe phenotype AATD. To our knowledge, no other study has directly investigated this relationship.

METHODS

Subjects

Through the Alpha-1 Foundation Research Registry, we recruited 500 self- reported patients with severe AATD (ZZ, SZ, Znull, FZ) to participate in our study. Although all data provided to the researchers were without patient identifiers and completely deidentified, the Alpha-1 Foundation Research Registry was able to confirm that all patients met appropriate severity for inclusion.

Intervention

Study data were collected and managed using Research Electronic Data Capture, a secure, Web-based application designed to support data capture for research studies.[15] Our study questions consisted of yes/no, multiple choice, and free text answers to allow for elaboration when necessary. Question content included demographic information, patient experiences with diagnosis, treatment experiences, and, when available, the role of the allergist/immunologist during the course of care.

Outcome

Data were assessed in Microsoft Excel (Redmond, WA). Participants who did not complete the survey in its entirety were excluded from analysis. When appropriate, subgroups were created to better describe the involvement of the allergist/immunologist.

Institutional review board approval

The study was approved by the Penn State Hershey Medical Center (study ID 0001081) and the Medical University of South Carolina (HR 9059) institutional review boards. All participants were provided informed consent before initiating the survey.

RESULTS

Demographic characteristics

Of the 500 severe phenotype participants recruited, 226 completed the survey in full (45% response rate). There was a slight predominance of females (females: n = 129 [57%] vs males: n = 97 [43%]) and participants had an average age of 59 years (range, 11-83 years). The most common AATD phenotypes were ZZ and SZ, with a much smaller cohort of FZ and Znull patients (Table I). The distributions of sex, age, and phenotype are consistent with previously published data from the Alpha-1 Foundation Research Registry.[16]

AATD Diagnosis

Although 192 participants (85% of the total) described themselves as symptomatic, only 16% of these individuals (n = 30) were diagnosed correctly when their symptoms initially presented. The most common alternative diagnoses were asthma (n = 70 [36%]), allergic disease (n = 46 [24%]), COPD (n = 44 [23%]), emphysema (n = 25, [13%]), and hepatitis (n = 4 [2%]). The average age at diagnosis was 49 years (range, 4-80 years), with an average of 8 years of preceding symptoms before the diagnosis. Notably, 31 patients (16%) were diagnosed after enduring 10 to 20 years of symptoms while another 27 (14%) had symptoms for longer than 20 years before receiving a diagnosis of AATD. Pulmonologists made the majority of diagnoses (n = 117 [52%]), with the remaining patients receiving a diagnosis in various other clinical settings including family medicine (n = 18 [8%]), gastroenterology (n = 16 [7%]), internal medicine (n = 10 [4%]), allergy/immunology (n = 8 [4%]), neurology (n = 3 [2%]), dermatology (n = 2 [1%]), and 1 patient each for cardiology, hematology, infectious disease, radiology, general surgery, and obstetrics/gynecology. Other avenues for diagnosis included family screening (n = 27 [12%]), self DNA testing (n = 8 [4%]), research studies (n = 6 [3%]), respiratory therapist (n = 4 [2%]), and 1 respondent who selected other.

A total of 64 participants (28%) reported having a concurrent diagnosis of asthma with their AATD at the time of completing the questionnaire. Three-quarter of participants (n = 49 [76%]) were diagnosed with asthma first, whereas the remaining individuals were split evenly between AATD diagnosed first (n = 7 [11%]) or asthma and AATD diagnosed at the same time (n = 8 [13%]).