

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

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This study was supported by a grant from CSL Behring (King of Prussia, Pa). CSL Behring had no input on study design, analysis, or manuscript preparation.

Conflicts of interest: T. Kelbel, D. Morris, and M. P. Henao have received research and travel support and fees for participation in review activities from CSL Behring. T. Craig has received research and travel support and fees for participation in review activities from CSL Behring; is past American Academy of Allergy, Asthma & Immunology Interest Section Leader; is a board member for American Lung Association of the Mid-Atlantic; is an advisory board member for Hereditary Angioedema Association of America; is director of the Alpha-1 Foundation Clinical Resource Center, Hershey, Pa; has received consultancy fees from CSL Behring, Dyax, Shire, Merck, Biocryst, Bellrose, and Novartis; has received research support from Shire, Dyax, Pharming, Merck, Genentech, GlaxoSmithKline, Grifols, Novartis, Sanofi Aventis, Boehringer Ingelheim, and Biocryst; has received lecture fees from CSL Behring, Dyax, Shire, and Grifols; and is coinvestigator for Asthmanet, National Heart, Lung, and Blood Institute. D Walker declares no relevant conflicts of interest.

Received for publication May 23, 2016; revised January 3, 2017; accepted for publication January 6, 2017.

Available online ■■

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2017.01.008>

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

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 1). 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%]).

TABLE I. Participants' characteristics

Demographic characteristics	n	%
Male	97	43%
Female	129	57%
Age (y), mean (range)	59	(11-83)
Phenotype	n	%
ZZ	169	75%
SZ	46	20%
Znull	4	2%
FZ	7	3%

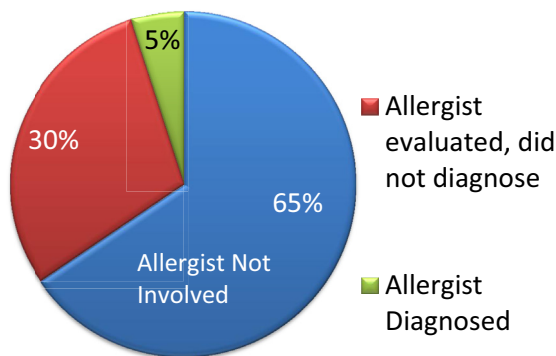


FIGURE 1. Allergist involvement in diagnosis.

Allergist involvement

Allergists were involved in the care of 78 patients (35% of our study population). Within this group, only 14% ($n = 11$) were tested for AATD (Figure 1). The initial diagnosis given by allergists in the other cases included allergic rhinitis/hay fever ($n = 31$ [40%]), asthma ($n = 25$ [32%]), no diagnosis/not allergic ($n = 9$ [12%]), COPD ($n = 4$ [5%]), sinus disease ($n = 3$ [4%]), and 1 patient each for venom allergy and common variable immunodeficiency (Figure 2). A total of 17 patients (22% of those who saw an allergist) were treated with immunotherapy (IT). Sixteen of these (94%) were on IT for more than 3 years before being diagnosed with AATD (Figure 3). Only 27 (35%) of the participants had spirometry performed as part of their allergist evaluation and 20 of these individuals reported being told their results were abnormal. Six participants reported that they had their spirometry followed for at least 3 years before the diagnosis of AATD (with 3 individuals for longer than 15 years). In addition, plethysmography was used in 16 cases and 14 recalled being told their results were abnormal. Only 1 subject reported being diagnosed with AATD as a direct result of the abnormal breathing test. With respect to asthma controller therapy, 28 (36%) were placed on inhaled corticosteroids before their AATD diagnosis. Thirty-two percent ($n = 9$) of these patients were treated for greater than 10 years.

Augmentation

Of all study participants, 157 (69%) had been prescribed alpha-1 antitrypsin replacement therapy, also known as augmentation therapy. Only 3% of this group ($n = 5$) had their augmentation therapy managed by an allergist (Figure 4).

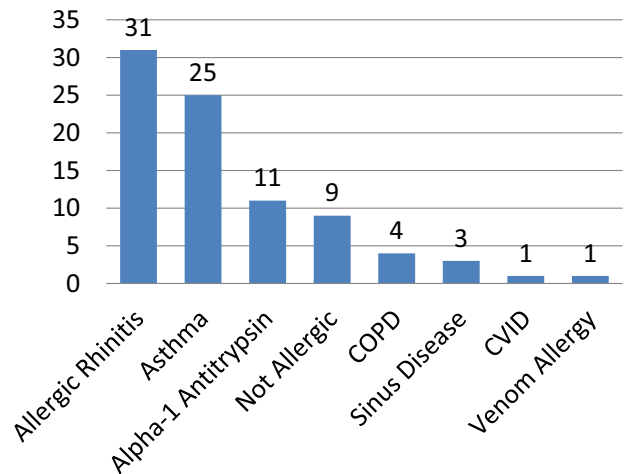


FIGURE 2. Most common diagnoses given by allergist. CVID, Common variable immunodeficiency.

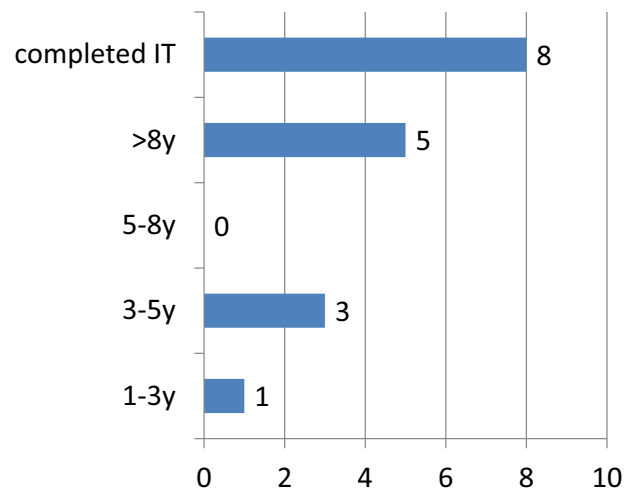


FIGURE 3. Years of IT before AATD diagnosis.

DISCUSSION

We believe our study is the first to specifically describe the involvement of the allergist/immunologist in the diagnosis and care of patients with severe AATD. Eden et al,¹⁷ however, previously reported on asthma and allergy in AATD. Although their study included nonsevere phenotypes, the prevalence of physician-diagnosed asthma was 44% and within the 458 ZZ phenotype subjects, the rate reached 50%.¹⁷ Similarly, 14% of ZZ individuals had been treated with allergy IT.¹⁷ Our results are consistent with this study and clearly show that patients with AATD are being evaluated by allergists/immunologists. More than one-third of our population was evaluated by an allergist/immunologist, but only 14% members of this group were screened for AATD. Our data are consistent with previous studies that demonstrated a significant delay in diagnosis for severely deficient phenotype patients.⁶

We suspect that patients with AATD are initially thought to have asthma or COPD; however, our results show that only 35% of patients reported having had spirometry performed by their

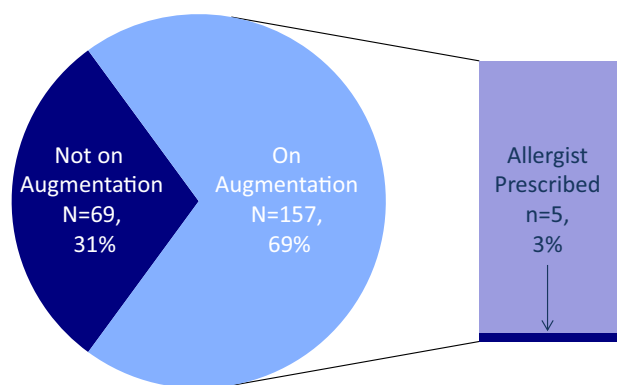


FIGURE 4. Augmentation prescribing.

allergist. Unfortunately, we are unable to determine whether any results from spirometry showed fixed obstructive disease, which would be indicative of the need to test for AATD. We were surprised that only one-third of our study participants received spirometry, and we believe that if all participants were screened with spirometry, more would have been diagnosed earlier with AATD. It is possible some of those unscreened were also under the care of a pulmonologist at the time; however, it seems unlikely this would be the case for the remaining 65% of participants because only 52% of our entire study population was diagnosed by a pulmonologist. In addition, 17 of our participants (22% of those who saw an allergist) were treated with IT and all but 1 were treated with IT for longer than 3 years before receiving a diagnosis of AATD. We propose that the failure to respond to IT would be an indication to consider AATD screening in patients with respiratory symptoms.

With respect to alpha-1 antitrypsin augmentation therapy, it is our opinion that allergist/immunologists are well suited to manage this aspect of patient care. The experience of the allergist/immunologist with other biologic therapies is broad with numerous immunoglobulin replacement options, c-1 esterase inhibitor replacement, and mAb therapies of omalizumab, mepolizumab, and reslizumab in asthma, with more therapies on the horizon. They are also well versed in patient-centered decision making regarding these expensive therapies. The 2016 AATD guidelines endorse augmentation therapy in severe phenotype individuals with an FEV₁ of less than or equal to 65% of predicted.¹⁸ However, for those with an FEV₁ of greater than 65%, a discussion regarding the potential benefit of reducing lung function decline versus the cost and lack of evidence for this benefit in this group is recommended.¹⁸ The report goes on to propose age, rapid decline in FEV₁, decreasing diffusion capacity, and progression of emphysema on imaging studies as important pieces of this discussion as the benefit of augmentation.¹⁸ In addition, allergists regularly see patients with inflammatory lung disease and are well trained in the preventative measures to lower disease risk (such as smoking cessation, vaccine promotion, and inhaled corticosteroid therapy).

Our study is not without limitations. Any retrospective survey has concerns for recall bias. In addition, some patients may have misread the questions. These misunderstandings may explain minor discrepancies in responses where initially 8 subjects indicated that they were screened by their allergist whereas later in the questionnaire 11 stated that their allergist screened them.

Regardless of the reasons for the discrepancy, the effect is minimal (allergist screening rate of 14% or 10%, respectively) and does not undermine the fact that increased screening for AATD is appropriate in the practice of allergy and immunology.

Overall, we hope that this study provides sufficient support for allergist/immunologists to reassess or initiate screening practices for AATD. The American Thoracic Society recommends that all subjects with asthma who have fixed obstructive disease, all patients with COPD, and patients with unexplained liver disease or bronchiectasis should be screened for AATD (alpha-1 antitrypsin serum level, alpha-1 antitrypsin protein phenotype, and/or alpha-1 antitrypsin genotype).¹ In addition, screening should take place in family members of affected patients, patients with necrotizing panniculitis, and patients with anti-proteinase 3-positive vasculitis (C-antineutrophil cytoplasmic antibody positive vasculitis).¹ Increasing the frequency of screening practices on patients meeting these criteria is a key step to help decrease the substantial delays in diagnosis many patients experience. It is important to mention that the pharmaceutical companies who manufacture alpha-1 augmentation therapy provide free patient screening kits using finger stick dried blood spot samples. Although it is clearly in their financial interest to increase the number of patients on augmentation therapy (especially with the significant cost of the drug), it is clearly to the patient's benefit to have the correct diagnosis made in a timely manner. In our practice, we generally use these free screening kits to save the patients the cost of the laboratory charge, but if pharmaceutical company contact is not desired or prohibited by institutional regulations, we would still strongly recommend screening appropriate populations. Ideally, screening includes genotype and serum protein levels. Early diagnosis of AATD will help physicians initiate treatment sooner and help prevent the progression to moderate and severe COPD as well as early mortality. In addition, we feel that allergists are well suited to manage alpha-1 antitrypsin augmentation therapy given their experience with other biologic medications such as C1-inhibitor and immunoglobulin therapy. Although allergists do not always manage severe COPD, the hope is that with early management of AATD many more patients will prevent or substantially delay moderate to severe COPD development, thus avoiding this concern.^{19,20}

We acknowledge the Alpha-1 Foundation Research Registry for its collaboration, the Research Electronic Data Capture consortium for use of its survey instrument, and CSL Behring for an unrestricted investigator-initiated small grant supporting this work.

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