COMMENTARY

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Alpha-1 antitrypsin deficiency: A persistently underrecognized condition

Alpha-1 antitrypsin deficiency is an autosomal codominant condition—2 versions of the gene contribute to a low alpha-1 antitrypsin serum level—that predisposes individuals to chronic obstructive pulmonary disease (COPD), liver disease (including cirrhosis and hepatocellular carcinoma), and panniculitis; it is also associated with cytoplasmic antineutrophil cytoplasmic antibody–positive vasculitis.[1–3] Population-based screening studies show that 1 in 3,500 individuals in the United States, or approximately 100,000 Americans, are homozygous for the Z allele, which causes the severe form of alpha-1 antitrypsin deficiency (the PI*ZZ type; see the sidebar, "How alpha-1 antitrypsin variants cause disease").[4] Yet, fewer than 15% of these individuals have been diagnosed with alpha-1 antitrypsin deficiency.

Indeed, underrecognition of alpha-1 antitrypsin deficiency has been stubbornly persistent since the disease was originally described in 1963.[5] Because only about 10% of patients with COPD see pulmonologists,[6] primary care clinicians hold the greatest opportunity to diagnose alpha-1 antitrypsin deficiency and address this underrecognition. Detecting alpha-1 antitrypsin deficiency early is imperative because diagnostic delay is associated with harm, including worsened clinical status and impaired survival.[7,8] Importantly, because alpha-1 antitrypsin deficiency is a genetically inherited condition, finding an affected individual provides an opportunity to detect and avert disease in affected family members.

In light of the call to action for internists and primary care clinicians to play a crucial role in detecting individuals with alpha-1 antitrypsin deficiency, this article discusses the evidence that alpha-1 antitrypsin deficiency is underrecognized and how that confers harm; briefly reviews strategies that have been undertaken to enhance detection, with emphasis on the notion that compliance with well-established alpha-1

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HOW ALPHA-1 ANTITRYPSIN VARIANTS CAUSE DISEASE

The protein alpha-1 antitrypsin is an antiprotease and anti-inflammatory molecule contained within the primary granules of neutrophils that neutralizes neutrophil elastase, a proteolytic enzyme. Of the more than 150 described variants of wild type, or normal, alpha-1 antitrypsin (called PI*MM, where PI stands for "protease inhibitor"), PI*ZZ is the genotype that accounts for more than 90% of lung and liver disease in alpha-1 antitrypsin deficiency.

The Z protein is distinguished by a single amino acid substitution—lysine for glutamic acid—at position 342.[1] In the liver, the Z protein folds abnormally and polymerizes within hepatocytes, resulting in intracellular accumulation of the variant alpha-1 antitrypsin. The accumulation of polymerized variant alpha-1 antitrypsin leads to hepatic fibrosis and sequelae,[1–3] and is considered a "toxic gain of function."

In contrast, when there is a lack of alpha-1 antitrypsin in the lungs, neutrophil traffic to the lung can lead to unopposed proteolysis, causing breakdown of alveolar walls and resulting in complications like chronic obstructive pulmonary disease or emphysema.[1–3] This is considered a "toxic loss of function."

TABLE 1
Alpha-1 antitrypsin deficiency diagnostic delay interval estimates in studies to date

Study	Year	Country	Diagnostic delay (years)[a]
Stoller et al[10]	1994	United States	7.2 ± 8.3
Stoller et al[11]	2005	United States	5.6 ± 8.5
Campos et al[12]	2005	United States	8.3 ± 6.9
Köhnlein et al[13]	2010	Germany	5.1 ± 6.3
Greulich et al[14]	2013	Germany	Median 7 (range 0–73, interquartile range 13)
		Italy	Median 6 (range 0–40, interquartile range 11)
Tejwani et al[7]	2019	United States	Median 5 (25%–75% confidence interval 2.9–15.4) for participants with symptoms
Meischl et al[8]	2023	Austria	Median 5.3 (interquartile range 2.2–11.5)

[a]Data presented as mean ± standard deviation unless indicated otherwise.

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antitrypsin deficiency management guidelines would enhance recognition; and provides an overview of emerging strategies to enhance recognition, including using artificial intelligence (AI).

ALPHA-1 ANTITRYPSIN DEFICIENCY IS STILL UNDERRECOGNIZED

Two major lines of evidence show that alpha-1 antitrypsin deficiency is severely underrecognized. First, patients with alpha-1 antitrypsin deficiency typically experience long delays between first presenting with symptoms attributable to the condition (commonly dyspnea) and receiving a diagnosis.[8–12] In other words, the diagnostic delay interval is frequently quite long, measuring 5 to 8 years in multiple studies over time (**Table 1**).[4,7,8,10–14] There is little evidence that this diagnostic delay is shortening.

The second observation is that patients often see multiple physicians before the diagnosis is made. In an early study, nearly 44% of patients with PI*ZZ alpha-1 antitrypsin deficiency saw at least 3 physicians before initial recognition, and 12.5% reported seeing at least 6 physicians before being diagnosed with alpha-1 antitrypsin deficiency.[10] Regrettably, more recent experience indicates that this pattern of underrecognition persists,[15] with one study reporting that 12% of patients saw 6 to 12 physicians before diagnosis.[16]

Contributing factors

There are several reasons for the persistent underrecognition of alpha-1 antitrypsin deficiency.

Knowledge gaps. First, alpha-1 antitrypsin deficiency awareness and fundamental knowledge of its pathogenesis and clinical manifestations are frequently lacking. Studies of pulmonologists, internists, and primary care clinicians in multiple countries have consistently shown that self-reported knowledge of alpha-1 antitrypsin deficiency often exceeds actual, performance-based knowledge.[17,18] As expected, knowledge among primary care clinicians is lower than that among specialists; however, specialists' knowledge has also been shown to be woefully lacking.

A lack of compliance with the many existing alpha-1 antitrypsin deficiency guidelines is a second contributor.[9,19,20] Reasons for guideline nonadherence generally include lack of familiarity with existing guidelines, an aversion to following guidelines (eg, a perception of "cookie-cutter medicine"), and the inertia of prior practice. Demographic and clinical features associated with a lower likelihood of being tested for alpha-1 antitrypsin deficiency include male sex, non-White race, former and current tobacco smoking, and older age.[21]

Therapeutic nihilism, a third contributor to underrecognition, is the (erroneous) belief that no effective therapy exists for alpha-1 antitrypsin deficiency and

therefore there is no imperative to make a diagnosis.[14] This flawed understanding also overlooks the critical fact that because alpha-1 antitrypsin deficiency is an autosomal codominant condition, first-degree relatives—siblings, biological children, and, when appropriate, parents—should also be tested (**Table 2**).[9] Identifying a proband can also benefit the health of their family members through simple measures like encouraging smoking cessation, occupational counseling to avoid exposure to heavy smoke or dust, and ongoing lung and liver function monitoring to facilitate early disease detection.

DELAYED DIAGNOSIS CONFERS HARM

Not surprisingly, as emphysema and liver fibrosis are progressive and worsen over time, delaying a diagnosis of alpha-1 antitrypsin deficiency confers harm. Tejwani et al[7] showed that individuals with alpha-1 antitrypsin deficiency with a delayed diagnosis had more severe lung disease, and the longer diagnostic delay was significantly associated with a higher St. George's Respiratory Questionnaire score (indicating worse functional status), higher COPD Assessment Test score (indicating worse health status), and a trend toward worsened airflow obstruction.

In a study from 2023, Meischl et al[8] showed that the mean diagnostic delay interval among 268 individuals with severe alpha-1 antitrypsin deficiency was 5.3 years and that those who experienced a diagnostic delay longer than 2 years had lower rates of overall survival and transplant-free survival.

CURRENT GUIDELINES FOR DIAGNOSTIC TESTING AND TREATMENT

Multiple guidelines[1,2,9,19] have specified when individuals should be tested for alpha-1 antitrypsin deficiency (**Table 2**). Most notably, every patient with fixed airflow obstruction on pulmonary function tests (defined as a ratio of forced expiratory volume in 1 second to forced vital capacity [FEV_1/FVC] < 0.7 or the lower limit of normal on postbronchodilator spirometry[19]) should be tested once for alpha-1 antitrypsin deficiency. This recommendation applies whether the patient has been diagnosed with COPD, emphysema, chronic bronchitis, or even asthma (as long as the airflow obstruction persists after bronchodilation). Therefore, all patients presenting to their primary care clinicians with dyspnea should undergo spirometry, with postbronchodilator testing if there is airflow obstruction as well as other pulmonary function tests as needed depending on clinical context.

TABLE 2
Testing recommendations for alpha-1 antitrypsin deficiency

All individuals with the following should be tested: • Chronic obstructive pulmonary disease, regardless of age or ethnicity • Unexplained chronic liver disease • Necrotizing panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis
Once an individual with an abnormal gene for alpha-1 antitrypsin is identified, testing should be offered to their parents, siblings, biological children, and extended family members; genetic counseling should also be provided
Only testing the serum alpha-1 antitrypsin level is not recommended for family members because it does not fully characterize disease risk from alpha-1 antitrypsin deficiency
Genotyping for at least the S and Z alleles is recommended for diagnostic testing of symptomatic individuals; advanced or confirmatory testing should include 1 or more of the following: protease inhibitor typing, serum alpha-1 antitrypsin level testing, and expanded genotyping

Based on information from reference 9.

Other guideline-recommended indications for alpha-1 antitrypsin deficiency testing include the following:

- The presence of otherwise unexplained liver disease, bronchiectasis, or both
- Necrotizing panniculitis
- Being a first-degree relative of an individual with alpha-1 antitrypsin deficiency.

Establishing a diagnosis

Diagnosing alpha-1 antitrypsin deficiency is generally straightforward and involves genotyping, checking the alpha-1 antitrypsin serum level, or both. Genotyping for the most common variant alleles—Z, S, I, and F—is generally performed with polymerase chain reaction. Normal alpha-1 antitrypsin serum levels range from 102 to 254 mg/dL, with individuals with PI*ZZ alpha-1 antitrypsin deficiency characteristically having serum levels about 30% to 50% of normal (29–52 mg/dL),[22] uniformly below the serum alpha-1 antitrypsin level of 57 mg/dL that is considered to be a protective threshold value.

Although the serum protective threshold value concept is an imperfect construct with noteworthy, albeit uncommon, exceptions, it has proven largely useful in diagnosing alpha-1 antitrypsin deficiency and determining those at risk of lung disease. Individuals with serum alpha-1 antitrypsin levels below 57 mg/dL

(eg, those with the PI*ZZ type) are usually considered to be at risk of developing emphysema, especially if they smoke, whereas those with serum alpha-1 antitrypsin levels above this protective threshold value are considered to be at lower risk.

Treatment recommendations

Once diagnosed, patients with alpha-1 antitrypsin deficiency are currently treated with a weekly infusion of purified pooled human plasma–derived alpha-1 antitrypsin, called *augmentation therapy*, which raises serum and lung alpha-1 antitrypsin levels to enhance the antiprotease protection, thereby addressing the toxic loss of function. The weight of evidence shows that augmentation therapy slows the progression of emphysema but offers no benefit for the liver disease resulting from the toxic gain of function.[1]

New treatments are under development, including those for alpha-1 antitrypsin deficiency–associated liver disease, interventions targeting protein conformational changes, gene therapy, and DNA and messenger RNA editing approaches.[4]

STRATEGIES TO ENHANCE RECOGNITION

As reviewed in detail elsewhere,[4] a variety of interventions have been undertaken to enhance recognition of individuals with alpha-1 antitrypsin deficiency.

- Strategies centered around education have included offering grand rounds, presentations at national meetings, and even targeted educational interventions in communities.
- Efforts to drive adherence to guidelines have been conducted by holding "testing events," issuing prompts in pulmonary function test reports to check for alpha-1 antitrypsin deficiency, and issuing best practice alerts in electronic medical records for individuals with guideline-indicated clinical features that should prompt testing.
- Patient-facing strategies have included sending notifications through an electronic portal to patients who receive a prescription for long-acting muscarinic agents with long-acting beta agonists indicated for COPD recommending that they undergo testing for alpha-1 antitrypsin deficiency and directing them to where they can obtain a free test.

Many of these strategies have had a modest effect, but have not shown lasting, scalable effectiveness.

Because available strategies have not meaningfully enhanced recognition of individuals with alpha-1 antitrypsin deficiency, several novel strategies are being explored.

Leveraging AI

AI algorithms running within an electronic medical record are being developed to identify individuals at risk of alpha-1 antitrypsin deficiency.[23–25] For example, Pfeffer et al[24] applied a machine learning algorithm to 21,381 records selected for a COPD diagnosis (of which about 4% were actual patient records vs other administrative records). The final model showed good diagnostic accuracy (area under the receiver operating characteristic curve 0.90).

More recently, preliminary findings by Stoller et al[25] describe the performance of an AI algorithm that was first developed in a large administrative database and then validated and further refined in a sample of 21,166 actual patient records. Testing the algorithm in a large number of actual patients in whom an alpha-1 antitrypsin deficiency diagnosis has been confirmed or ruled out better replicates a real-world experience, and confirmation is now ongoing. Specifically, follow-up studies are deploying the AI algorithm in real-time practice. In these studies, physicians are prompted to test for alpha-1 antitrypsin deficiency when the algorithm flags a patient with features that suggest the condition. Outcome measures will include the following:

- How many tested patients actually have alpha-1 antitrypsin deficiency
- The frequency with which physicians comply with the prompts to test for alpha-1 antitrypsin deficiency
- How many patients found to have alpha-1 antitrypsin deficiency lack clinical features that would have prompted testing according to current guidelines[1,2,9,19] (**Table 2**).

To date, the AI algorithm has shown a strong performance (area under the receiver operating characteristic curve 0.89),[25] though further study is needed to fully clarify the diagnostic accuracy of using AI to detect alpha-1 antitrypsin deficiency (eg, false positives remain a concern).

AlphaDetect

A second promising development to enhance detection is the recent formation of an organization called AlphaDetect (alpha1.org/alphadetect). AlphaDetect is a not-for-profit subsidiary of the Alpha-1 Foundation, a patient support organization committed to improving the lives of affected individuals and finding a cure for alpha-1 antitrypsin deficiency. AlphaDetect was organized to ensure that all individuals with alpha-1 antitrypsin deficiency are detected. It will offer free testing and, in concert with the Alpha-1 Foundation, genetic counseling services.

KEY TAKEAWAYS

Several lines of evidence support the imperative for primary care clinicians to suspect and test for alpha-1 antitrypsin deficiency:

- Alpha-1 antitrypsin deficiency is severely and persistently underrecognized and can cause significant morbidity and mortality.[1]
- Most patients with COPD, the most common clinical consequence of severe alpha-1 antitrypsin deficiency, are cared for by primary care clinicians and do not see pulmonologists.[6]
- Family members of individuals diagnosed with alpha-1 antitrypsin deficiency may also have unsuspected alpha-1 antitrypsin deficiency and should be tested.[9]
- Specific therapy exists for COPD attributable to alpha-1 antitrypsin deficiency, and other promising treatments are under active investigation.[1,2,4]

Taken together, these factors underscore the paramount importance of the primary care clinician in detecting patients with alpha-1 antitrypsin deficiency to address this important, unmet clinical need.

DISCLOSURES

Dr. Stoller has reported consulting for CSL Behring, Genzyme/Sanofi, Gondolabio NA, Grifols, InhibRx, Korro, Lupin Pharmaceuticals, Takeda, UpToDate, and Vertex Pharmaceuticals; teaching and speaking for CSL Behring and Grifols; and serving as a research principal investigator and co-principal investigator for Takeda.

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