REVIEW

JAMES K. STOLLER, MD, MS*
Professor of Medicine, Cleveland Clinic Lerner College of Medicine of the Case Western Reserve University; Vice Chairman, Division of Medicine, Cleveland Clinic; Head, Section of Respiratory Therapy, Department of Pulmonary, Allergy, and Critical Care Medicine, Cleveland Clinic

LEONARD FROMER, MD*
Assistant Clinical Professor, Family Medicine, David Geffen School of Medicine, The University of California at Los Angeles

MARK BRANTLY, MD*
Professor of Medicine, Molecular Genetics, and Microbiology, Division of Pulmonary and Critical Care Medicine and Department of Biometry, University of Florida College of Medicine; Director, University of Florida Alpha-1 Antitrypsin Genetics Laboratory, University of Florida College of Medicine, Gainesville

JAMES STOCKS, MD*
Professor of Medicine, Director of the Pulmonary Function and Sleep Laboratories, University of Texas at Tyler

CHARLIE STRANGE, MD*
Professor, Pulmonary and Critical Care Medicine, Medical University of South Carolina, Charleston

Primary care diagnosis of alpha-1 antitrypsin deficiency: Issues and opportunities

ABSTRACT

Alpha-1 antitrypsin deficiency—an autosomal co-dominant condition that predisposes to emphysema and also to liver disease—affects 100,000 Americans, yet in many cases the condition is either not diagnosed or the time between first symptoms and diagnosis is long. Because primary care physicians care for large numbers of patients with chronic obstructive pulmonary disease, enhanced suspicion of and testing for alpha-1 antitrypsin deficiency in the primary care setting would help identify people affected with this condition. The authors discuss impediments to diagnosis and drivers to making the diagnosis of alpha-1 antitrypsin deficiency, and they suggest several measures to enhance clinicians' recognition of the condition.

KEY POINTS

Severe deficiency of alpha-1 antitrypsin can be associated with obstructive lung disease, chronic liver disease, and panniculitis, and with vasculitis positive for C-antineutrophil cytoplasmic antibody (including Wegener granulomatosis).

A "pay for performance" program in which rewards are conferred for testing all patients with chronic obstructive pulmonary disease would likely enhance clinicians' recognition of alpha-1 antitrypsin deficiency and shorten the delay to diagnosis.

*Dr. Stoller has indicated that he has been a consultant for Talecris and Baxter corporations. Dr. Brantly has indicated that he has received honoraria from Talecris. Dr. Strange has indicated that he has been a consultant for Talecris, GTC Biotherapeutics, and Arriva.

BECAUSE ALPHA-1 ANTITRYPSIN deficiency is still persistently underrecognized, we clearly need strategies to enhance recognition of this condition, which predisposes to emphysema and also to liver disease, so that we can offer patients and their affected family members the benefits of therapy. The pool of unrecognized patients includes those with chronic obstructive pulmonary disease (COPD), and since primary care physicians care for many of these patients, primary care physicians can play a key role in identifying patients with alpha-1 antitrypsin deficiency.

We believe that by systematically considering drivers of physician behavior and by designing incentives that address these drivers, useful strategies to enhance the diagnosis of alpha-1 antitrypsin deficiency will be found. Our hope in this discussion is to stimulate our colleagues to watch for this condition, to consider impediments to its diagnosis, and to find ways to incorporate testing for it into regular clinical practice.

HOW PREVALENT IS IT, AND WHO IS AT RISK?

Alpha-1 antitrypsin deficiency is a common, autosomal co-dominant condition that predisposes to emphysema[1,2] and, for the most common severely deficient phenotypes (eg, PI*ZZ), also to liver disease. Available estimates suggest that the prevalence of severe deficiency of alpha-1 antitrypsin (ie, PI*ZZ) in the United States is about 1 in 3,000, so that approximately 100,000 Americans are

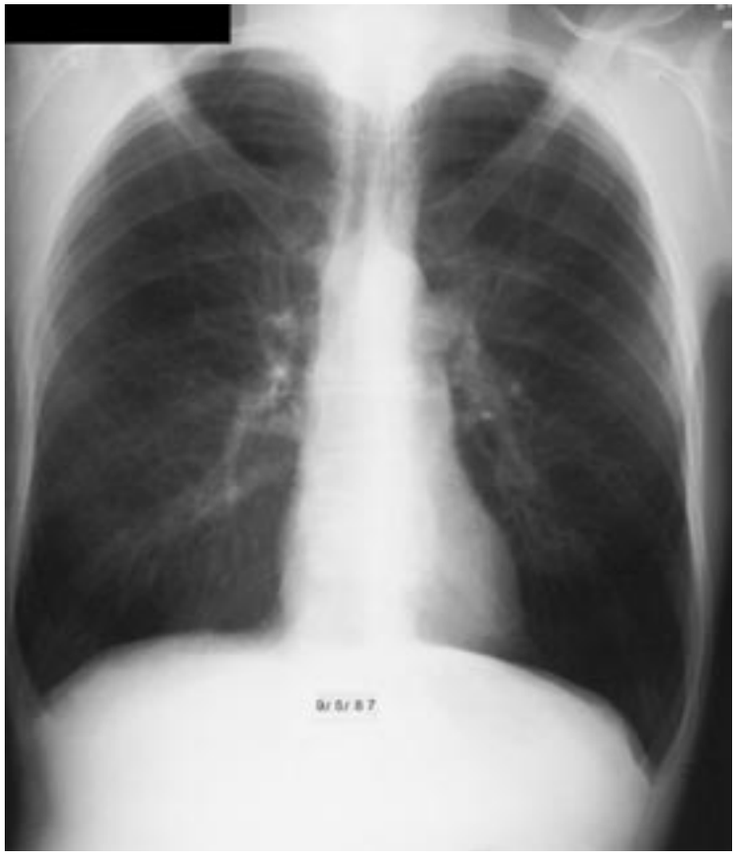

FIGURE 1. Posteroanterior chest radiograph of a patient with severe deficiency of alpha-1 antitrypsin (PI*ZZ phenotype). Hyperinflation is demonstrated by flattening of the diaphragm. Note that the hyperlucency is more evident at the base of the lungs than at the apex. This finding is characteristic and suggestive of alpha-1 antitrypsin deficiency but is seen in only a minority of chest radiographs.

severely deficient.[1,2] Furthermore, among whites, the prevalence of carriers (heterozygotes) of the most common severe deficiency allele, the so-called Z, is approximately 2% to 3%, suggesting that approximately 8 million Americans have an at-risk allele.

RED FLAGS

How would the primary care physician recognize a patient with alpha-1 antitrypsin deficiency? Severe deficiency of alpha-1 antitrypsin (as in the PI*ZZ type) can be associated with obstructive lung disease, chronic liver disease (with a spectrum of presentations from neonatal jaundice to cirrhosis and hepatoma), and panniculitis (an inflammatory disease of the subcutaneous tissue presenting with ulcerating and often painful skin lesions), and with vasculitis positive for C-antineutrophil cytoplasmic antibody (C-ANCA) (including Wegener granulomatosis).

Nevertheless, the clinical presentation of alpha-1 antitrypsin deficiency can be subtle, as people with this deficiency may not "look" different than other patients with COPD or cirrhosis. Still, certain features should surely heighten the suspicion of alpha-1 antitrypsin deficiency: namely, onset of airflow obstruction before age 50, emphysema associated with a radiographic pattern of basilar hyperlucency (**FIGURE 1**) (as opposed to the usual pattern of apical hyperlucency seen in smoking-related emphysema), a family history of liver or lung disease, and emphysema occurring in a nonsmoker or very light smoker.

While suspicion and testing for alpha-1 antitrypsin deficiency should extend far more broadly than these circumstances (as discussed below), these features should certainly and especially prompt the primary care physician to test for it.

In fact, indications for testing for alpha-1 antitrypsin deficiency with an inexpensive blood test (ie, for a serum alpha-1 antitrypsin level) were published by the American Thoracic Society and the European Respiratory Society in 2003 (**TABLE 1**).[1] Notably, **TABLE 1** presents the groups for whom testing is strongly recommended in this evidence-based guideline document (ie, with a so-called type A recommendation). Initial testing can include a serum level only. As a working rule, when the serum level is below 100 mg/dL (normal ranges vary but are generally > 100 mg/dL), additional blood testing for a phenotype (to characterize the alleles present in the individual being tested) is recommended in order to identify individuals with severe deficiency of alpha-1 antitrypsin. The so-called PI*ZZ phenotype is the most common severe deficient variant, accounting for more than 90% of people with severe alpha-1 antitrypsin deficiency[2] and based on a single amino acid substitution (of lysine for glutamic acid at position 342 of the 394 amino acid glycoprotein that is alpha-1 antitrypsin).[2] After arranging for testing of liver and pulmonary function for such patients, the primary care physician may consider referring these patients

TABLE 1

Indications for testing for alpha-1 antitrypsin deficiency based on available guidelines

Symptomatic adult with persistent obstructive defects on pulmonary function testing, whether labeled as emphysema, chronic bronchitis, or asthma, and in a geographic location where the expected prevalence of alpha-1 antitrypsin deficiency is at least 1 in 3,000 (as it is in the United States)

Asymptomatic individual with persistent obstructive pulmonary dysfunction on testing, who smokes or used to smoke, or who has occupational exposure predisposing to lung disease

Adult with necrotizing panniculitis

Sibling of a family member with PI*ZZ or other severe form of alpha-1 antitrypsin deficiency, with "severity" based on the serum level being below 11 micromolar or approximately 50 mg/dL using a nephelometry assay, not based on lung function (ie, a person can have severe deficiency of alpha-1 antitrypsin but normal lung function)

ADAPTED FROM AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY. STANDARDS FOR THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ALPHA-1 ANTITRYPSIN DEFICIENCY. AM J RESPIR CRIT CARE MED 2003; 168:816–900.

to knowledgable consultants as well as to excellent patient resources, such as those offered by the Alpha-1 Foundation (**www.alphaone.org**), the Alpha-1 Association (**www.alpha1.org**), and the American Thoracic Society (**www.thoracic.org**).

Because alpha-1 antitrypsin deficiency is common, attention has focused recently on impediments to diagnosis and on the long delays in establishing the diagnosis. For example, survey data from 2003 suggest that for affected individuals the mean duration between the first symptom and the initial diagnosis was 8.4 (standard deviation ± 6.9) years,[3,4] no shorter than the diagnostic delay interval that was described in a similar survey 10 years earlier.[5] Furthermore, results from recent studies regarding the mean number of physicians seen between the first symptom and the diagnosis show that patients saw 2.7 ± 2.4 physicians before diagnosis and that 20% saw at least four physicians before the diagnosis was established.[4]

Given the persistent underrecognition of alpha-1 antitrypsin deficiency,[6] attention has turned to strategies to enhance detection, especially because effective health interventions for this condition are available[7] and because the diagnosis of this autosomal codominant condition may have an impact on other family members (**TABLE 2**).[1,2,7] Because many patients with COPD are seen and managed by primary care physicians and because it is the primary care office that enhances care of the entire family unit,[8] this attention has naturally focused on strategies to enhance detection of alpha-1 antitrypsin deficiency by primary care physicians.

In the rest of our discussion we consider both impediments to and ways to enhance the recognition of alpha-1 antitrypsin deficiency.

Patients may not 'look' different than others with COPD or cirrhosis

IMPEDIMENTS TO MAKING THE DIAGNOSIS

We suspect three main impediments to making the diagnosis of alpha-1 antitrypsin deficiency:

- Physicians lack awareness and knowledge of the condition, thereby precluding suspicion of the condition and testing of patients at risk
- Office work flow may not be conducive to testing for this condition, eg, lack of personnel, poor communication between clinicians and support personnel, lack of awareness of which test to order (eg, phenotype, serum level), and lack of access to testing methods
- "Therapeutic nihilism," ie, the belief by some physicians that there is no effective therapy for alpha-1 antitrypsin deficiency, so that identifying these patients offers no clinical benefit. However, this line of reasoning overlooks the fact that therapy can

TABLE 2

Possible benefits and risks of testing for alpha-1 antitrypsin deficiency

Benefits
Assist in smoking cessation
Assist in occupational decisions to avoid dusty environments
Provide meaningful genetic data to family members
Provide disease-specific support through national support and advocacy groups
Offer augmentation therapy specific for alpha-1 antitrypsin deficiency
Risks
Insurance or job discrimination after the diagnosis is made
Discovery of genetic information that could be harmful to family unity

offer benefit[1,7] and that, as a genetic disease, alpha-1 antitrypsin deficiency can also profoundly affect family members of the proband.

Given these potential impediments to the diagnosis of alpha-1 antitrypsin deficiency, we consider several drivers for making the diagnosis that address these impediments.

Organize the office work flow to encourage testing for alpha-1 antitrypsin deficiency

DRIVERS FOR MAKING THE DIAGNOSIS

Enhancing diagnosis in practice generally requires the convergence of two events:

- Assuring adequate knowledge of the condition by the clinician
- Embedding into the clinician's daily practice a process that encourages making the diagnosis.

In the case of alpha-1 antitrypsin deficiency, this convergence requires that clinicians receive and incorporate information about its clinical manifestations and presentation and that they organize the office work flow to encourage appropriate suspicion and testing for it in everyday practice. Given the time pressures of current practice, knowledge alone without a facilitative work flow will not permit making the diagnosis. Similarly, a facilitative work flow without diagnostic suspicion or acumen will not allow diagnosis.

Forces that shape practice behavior

Another lens through which to analyze potential drivers of the diagnosis of alpha-1 antitrypsin deficiency in primary care practice regards the forces that shape physician practice behaviors. We consider four such forces:

- Physician-centered behaviors—eg, those related to incentives, including reimbursement drivers to physician practice, physicians' desires to practice state-of-the-art medicine, competitiveness, fear of litigation related to missed diagnosis
- Patient-driven factors—eg, patients' desire to undergo testing for alpha-1 antitrypsin deficiency
- Population-based screening that detects disease
- Technology-based drivers of diagnosis—eg, use of algorithms to suggest diagnoses that are programmed into the electronic medical record or generated by diagnostic testing equipment, eg, pulmonary function testing equipment, including greater use of office-based spirometry by primary care physicians.

How can each of these drivers of diagnosis be harnessed to enhance the diagnosis of alpha-1 antitrypsin deficiency by primary care physicians?

With respect to physician-centered behaviors, to the extent that reimbursement can powerfully drive physician behavior, aligning financial incentives to maximize reimbursement when alpha-1 antitrypsin deficiency is found should encourage diagnosis. For example, if diagnosing the condition were part of a "pay for performance" program in which rewards were conferred for testing all patients with COPD (as officially advocated by several professional respiratory societies),[1] clinicians' recognition of alpha-1 antitrypsin deficiency would likely be enhanced and the delay to diagnosis[3–5] would likely be shortened.

Similarly, in a health maintenance organization environment, if diagnosis of alpha-1 antitrypsin deficiency prompted smoking ces-

sation and an associated decrease in both unscheduled outpatient visits and resource utilization, system savings might be shared with the physician. Again, the incentive of sharing saved revenue would be expected to enhance testing for alpha-1 antitrypsin deficiency.

Other physician-centered drivers of the diagnosis of this condition include physicians' strong desire to practice the best, most thorough medicine, a competitive desire not to be outdone by colleagues who are testing, and the desire to avoid litigation related to missing the diagnosis.

Patient drivers are a second encouragement for physicians to test for alpha-1 antitrypsin deficiency. For example, if all patients with COPD requested testing for alpha-1 antitrypsin deficiency on seeing their primary care physician, service-oriented clinicians would likely test for it liberally. Similarly, if patients chose their primary care physician based on knowledge of their physician's likelihood to test for this and other common conditions, physicians seeking patients would test liberally and encourage a reputation of testing in their practice.

A third potential driver of enhanced diagnostic testing for alpha-1 antitrypsin deficiency is a public policy that would mandate testing the entire population, perhaps at birth, as in the case of testing newborns for phenylketonuria, which has a prevalence several times lower than that of alpha-1 antitrypsin deficiency.[9] Indeed, such population-based testing programs have been undertaken on a large scale both in the United States, where 107,033 consecutive newborns were tested,[9] and in Sweden, where 200,000 consecutive newborns were tested.[10]

While population-based testing can be effective in identifying people with alpha-1 antitrypsin deficiency, current impediments to adopting such screening include concerns about the impact on insurability and employability of those detected to have a risk,[1] concerns about the societal cost associated with widespread screening,[11] and uncertainty about the cost-effectiveness of screening. Thus, another public policy driver of enhanced detection of alpha-1 antitrypsin deficiency detection would be stronger legislation to prohibit discrimination based on genetic information.

Finally, in the era of widespread use of the electronic medical record, focused use of technology could encourage specific clinical practices, such as testing for alpha-1 antitrypsin deficiency. For example, if physicians were prompted to consider this condition when they received the results of pulmonary function tests showing fixed airflow obstruction, testing for alpha-1 antitrypsin deficiency would likely increase. Also, if eliciting a family history of COPD or chronic liver disease prompted a physician alert on the electronic medical record to test the serum alpha-1 antitrypsin level, testing for this deficiency would likely increase. Finally, as has been advocated, if office-based spirometry were more widely used by primary care physicians,[12,13] greater detection of COPD would perhaps prompt greater suspicion of and testing for alpha-1 antitrypsin deficiency.

Indeed, pilot studies of these interventions are currently under way. For example, Rahaghi et al[14] found in a small pilot study that the frequency of testing increased when a suggestion for testing for alpha-1 antitrypsin deficiency was included on the pulmonary function test reports of COPD patients. Also, the Alpha-1 Foundation is currently launching a study to evaluate the impact of pulmonary function test technicians' inviting COPD patients to undergo alpha-1 antitrypsin testing at the time of pulmonary function testing.

The electronic medical record could prompt testing for deficiency

Other means

Other potential interventions include the conventional steps of developing and offering continuing medical education lectures (in person or Internet-based) and problem-based learning (eg, through case studies or clinical vignettes), perhaps incorporated into continuing medical education activities of official societies like the Society of General Internal Medicine or the American College of Physicians. Another strategy to promote testing is to empower patients by making high-quality, comprehensible information available, as in the brochures for patients and families prepared by the Alpha-1 Foundation (**www.alphaone.org**) and AlphaNet (**www.alphanet.org**). ■

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ADDRESS: *James K. Stoller, MD, MS, Department of Pulmonary, Allergy, and Critical Care Medicine, A90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail stollej@ccf.org.*

CME ANSWERS

Answers to the credit test on page 919 of this issue

1 **B** 2 **A** 3 **C** 4 **D** 5 **C** 6 **B** 7 **B** 8 **E** 9 **D** 10 **D** 11 **A** 12 **B**