Alpha-1 Antitrypsin Deficiency: Whom to Test, Whom to Treat?

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ABSTRACT

Alpha-1 antitrypsin deficiency (AATD) is the major identified genetic risk factor for chronic obstructive pulmonary disease (COPD). The biochemical events leading to lung destruction in AATD are well understood, and most of our understanding of the pathogenesis of COPD in general has been acquired through the study of AATD. There is a growing appreciation that early diagnosis of AATD can affect the course of disease and allow for appropriate treatment decisions to be made. Although there is published guidance regarding testing and treatment of AATD, the impact of this guidance has been minimal. AATD is underdiagnosed, and the evidence for current treatment recommendations is not without controversy. This article reviews the current recommendations for testing and treatment of AATD. Some of these recommendations are expected to change as legislation to prevent genetic discrimination is refined and new therapies for this relatively common genetic predisposition are developed. Additional genetic modifiers of COPD will be found, and the path set by AATD will facilitate their incorporation into our future management of COPD.

KEYWORDS: Alpha-1 antitrypsin deficiency, chronic obstructive pulmonary disease, emphysema, genetic testing, augmentation therapy
AAT is a very effective protease inhibitor, and it is almost unique in its ability to protect the protein elastin from degradation by serine proteases. The most potent endogenous elastin degrading protease in humans is the elastase produced by the human neutrophilic leukocyte, human neutrophil elastase (HNE). HNE is capable of degrading an array of different proteins in addition to elastin, but it is elastin degradation that leads to emphysema in humans. At the alveolar level, AAT is the major inhibitor of HNE in the lungs, and its deficiency puts the lungs at increased risk of elastin destruction and emphysema progression.

Detection of AATD has several advantages for those affected. Detecting an individual with AATD also detects a family at risk. The lung disease associated with AATD, just as with more usual COPD, is treatable through the removal of risk factors, prevention and treatment of exacerbations, improvement of fitness and diet, symptom management, and provision of supplemental oxygen when indicated. In addition, in appropriate individuals with lung disease due to AATD, there is specific therapy that can slow or prevent additional lung injury.

There is guidance regarding testing for AATD as well as recommendations regarding treatment. The evidence behind these recommendations is imperfect but growing. Exploring who to test and who to treat should improve the care of an important subgroup of individuals with COPD.

**NOMENCLATURE**

Historically, the mutations of the AAT gene and the proteins these genes produce have been named using letters of the alphabet. This dates back to the 1960s when AAT proteins were evaluated using potato starch gel electrophoresis. These gels were designed to migrate the AAT proteins so that the normal protein moved to the center of the gel while the most commonly identified deficient protein barely moved. The normal protein was labeled “M” and this deficient protein was labeled “Z.” As additional abnormal AAT proteins were identified, they were added to the list with their labels based on their migration in this gel system. Eventually, all the letters of the alphabet were used, and newly identified abnormal proteins were labeled according to their nearest neighbor in the gel with an added subscript usually representing the city of discovery, as in \( M_{Malton} \).

Isotypes of the normal M protein are now represented by subscript numerals, as in \( M_{2} \) and so forth. This nomenclature system has been called the protease inhibitor (PI) system. The various genes or their protein products are labeled in this system as PI\( Z \) or PI\( M \), for example.

Finally, there is a group of mutations that lead to the production of no AAT protein or only fragments of AAT protein. These are the Null mutations and in the PI system are labeled as "0," often followed by a number, even though there is no protein to migrate in a gel (see later discussion). Approximately 20 of these Null mutations have been found to date, and individuals unfortunate enough to have two Null mutations often develop emphysema at a very early age but have no protein accumulation in the liver and no apparent risk of liver disease.

**HOW TO TEST**

Recommendations regarding testing of individuals for AATD are complicated by the variety of testing methodologies available. There are three primary testing methods: (1) testing the blood to determine the quantity of AAT protein per volume (level testing), (2) testing the blood to evaluate the migration pattern of AAT protein in an isoelectric focusing gel between pH 4.0 and 5.0 (Pi-typing or phenotyping), and (3) evaluating an individual's DNA for common AAT mutations (genotyping). Each provides different information and often two or three tests are ordered on the same patient.

Level testing is certainly the least expensive and the most widely available. A severely deficient blood level (less than 50% of the lower limit of normal) provides clear evidence of AATD. The issue with level testing is the information it does not provide. Level testing is poor at identifying individuals carrying a single abnormal AAT gene because the level in AAT heterozygotes can be close to or within the normal range. Level testing will
not provide any information about the mutations involved, although individuals with severe deficiency are often assumed to have the Z mutation. Level testing will not identify those with AAT mutations that lead to normal levels of a dysfunctional AAT protein, although these mutations appear to be extremely rare.

Pi-typing will identify normal and abnormal AAT proteins of all types and is capable of detecting those 30 or so rare AATD-causing mutations, including those that lead to a dysfunctional protein. However, the preparation and interpretation of Pi-typing gels is as much an art as a science and requires the hands and eyes of experienced personnel. In addition, Pi-typing will not identify Null mutations because those mutations do not produce any circulating protein. Thus Pi-typing will not distinguish an individual with a ZNull genotype from one with a ZZ genotype.

Genotyping might be assumed to be the preferred test for individuals with a genetic condition. However, as currently performed, genotyping for AATD evaluates the genetic material of those tested for the presence of sequences specific for the Z and the S mutations. If neither is found on either of the two AAT genes, the patient is identified as MM or normal. A single Z or S genetic sequence will be reported as MZ or MS, respectively. Similarly, genotyping can also identify ZZ, SS, and SZ individuals. Any of the 30 to 40 rarer deficiency genes will be reported as M (not Z and not S). Null genes will be reported as M for the same reason. Performing simultaneous level testing can avert some of these false-negative results. A severely low level of AAT in the blood in someone identified as MZ by genotyping could suggest the presence of a ZNull or a Z combined with another severely deficient AAT gene and prompt further testing.

When rarer AATD genotypes are suspected, there are several laboratories in the United States that have prepared specialized probes for some of the rarer and Null genotypes and have the capability of doing rapid gene sequencing of the AAT gene.

WHOM TO TEST

Testing recommendations have changed over the years since AATD was first described in 1963. At the time of this initial description, AATD was thought to be a disease of individuals with a family history of precocious emphysema. Sufferers were thought to develop emphysema as young adults, and their emphysema was destined to have a rapid downhill course. Thus testing was limited to those with a history of "familial emphysema."

A 1969 publication pointed to AATD as a cause of liver failure in infants. Infants and children with otherwise unexplained liver disease were added to the list of those who should be tested for AATD.

A guidance document published in 1989, as well as a variety of more recent COPD standards, suggests that individuals with COPD or emphysema should be tested for AATD if disease onset occurs during the first several decades of adult life, especially if the disease is out of proportion to the smoking history or there is a family history of COPD.

In 2003, a widely endorsed, evidence-based document was published that recommended testing of all individuals with COPD for AATD. Although the overall impact of this recommendation on testing practices has been minimal, in centers where COPD patients have been tested regardless of age or family history, a large number of older individuals with COPD and AATD have been identified.

These current testing recommendations include the following:

- Testing all individuals with a diagnosis of COPD
- Testing all adults with asthma that does not completely reverse with maximal medical therapy
- Testing all individuals with unexplained liver disease
- Testing family members of those diagnosed with AATD

Family testing has a higher likelihood of revealing a positive result than the other recommendations already listed. The Alpha-1 Foundation and Alpha-1 Association have recently begun a family testing initiative that is designed to help inform family members about the benefits and potential risks of testing for AATD.

Finally, an open question is whether birth screening for AATD might be advisable. Such testing would certainly help identify, over several decades, most of those with AATD. Whether such testing provides sufficient benefit to justify the resources required remains to be determined.

WHOM TO TREAT

Once an individual is identified with AATD, decisions regarding treatment follow. For those with this genetic condition who do not have disease, there is no treatment indicated at present. Careful follow-up for emergence of lung, liver, or other associated conditions is the norm.

For those with AATD-related liver disease, currently no AATD-specific therapy is available. The liver disease appears to be due, at least in part, to the accumulation of abnormal AAT protein within the endoplasmic reticulum of hepatocytes. Although there is no therapy that can reduce this accumulation, this is an area of intense investigation. When AATD-related liver disease occurs, standard medical therapy for liver injury, cirrhosis, portal hypertension, and liver failure is employed. In the most severe cases, liver transplantation can be curative.
The more difficult treatment decisions are those surrounding the lung disease of AATD. In countries where it is approved, augmentation therapy is often considered. Augmentation therapy, the intravenous administration of purified, concentrated, human plasma-derived AAT protein, usually on a weekly basis, raises the blood and lung levels of AAT. The expectation is that increasing the available normal AAT protein in the blood and lung will slow or halt the progression of lung disease in those with emphysema due to AATD.

Before any consideration of augmentation therapy, other risk factors for disease progression need to be eliminated. Most importantly, personal tobacco smoking and exposure to secondhand smoke need to be eliminated. Occupational exposures to dusts, smokes, and fumes should be reduced or eliminated. Only when lung disease continues to progress following the elimination of such risk factors should augmentation therapy be considered, although the documentation of such progression can be problematic.

The initial evaluation of augmentation therapy relied on measurement of AAT protein levels in blood and bronchoalveolar lavage as the end point of clinical trials. Clinical efficacy could not be studied because of the small number of AATD patients identified in those days (early 1980s) and the long duration of observation required (3 to 5 years). Still, regulatory authorities in the United States and several European countries approved the marketing of augmentation therapy based on its biochemical rationale. In countries where it is approved, augmentation has become the standard of care for individuals with emphysema due to AATD. Because its effects are essentially prophylactic in nature, augmentation therapy was considered for all individuals with AATD, including those without any lung disease. This approach was discarded because (1) many individuals with AATD will never develop lung disease, (2) augmentation therapy is a blood product and therefore has potential adverse effects and limited supply, and (3) augmentation therapy is expensive.

The first documentation of clinical efficacy came during the analysis of registry data in the United States and Germany (in comparison with Danish patients). Although neither registry was designed to evaluate the efficacy of augmentation therapy, each was able to analyze its patient data in case-controlled, post hoc studies comparing individuals receiving and not receiving augmentation therapy. Each study found beneficial effects of long-term augmentation therapy usage. The U.S. registry demonstrated benefits that included increased survival and reduction in the rate of decline of lung function. The considerably smaller German registry did not note a survival benefit but did confirm the reduction in lung function decline. The most significant beneficial clinical results were seen in the group of patients whose initial forced expiratory volume in 1 second (FEV₁) was in the range between 35 and 49% of predicted and 31–65% of predicted (depending on the study).

Subsequent studies, including a recent meta-analysis, have tended to confirm these initial results. Although much has been made of the significance of the initial FEV₁ values in making treatment decisions, it should be recalled that these were not randomized trials, and the numbers of subjects at the extremes of pulmonary function were small. It is well described that the rate of decline of lung function in COPD patients tends to decrease as severity increases, making improvements in rate of decline more difficult to measure in the most severe group. Those whose lung function was in the midrange of severity, where the most significant improvements were seen, passed through milder levels of obstruction on their way to this moderately obstructed group. Should therapy be denied to individuals with mild emphysema due to AATD to watch them develop more severe emphysema so that therapy can be initiated?

To date, there has not been a definitive, randomized, masked, placebo-controlled, well-powered clinical efficacy trial of augmentation therapy. This makes it difficult to accept augmentation therapy as having proven efficacy. However, the preponderance of evidence collected has documented the benefits of augmentation therapy. In contrast, the cost–benefit analyses of these data have documented the great expense of life-years saved.

CONCLUSIONS
We are left with several challenges when discussing testing and treatment for AATD. Questions regarding the effectiveness of existing and future therapies can only be resolved through large, well-designed studies. There are currently too few patients with disease willing to participate in such efficacy trials. Detection of the thousands of undiagnosed individuals with AATD will certainly facilitate enrollment in such studies.

In contrast, detection efforts are often thwarted because physicians ask, Why test when the therapies available are not proven to be effective? What are the benefits of testing without a proven intervention?

The benefits of detection go beyond decisions regarding augmentation therapy, however. Education about AATD, including a broad understanding of disease mechanisms and risk, can help newly diagnosed patients obtain appropriate follow-up and treatment of their medical conditions. Family testing combined with genetic counseling can help an entire family avoid risk factors and monitor for disease. As additional genetic modifiers of COPD risk are identified, AATD will be viewed as the model system, and its testing and treatment guidelines may find even wider application.
REFERENCES