BEST PRACTICES IN: Diagnosis and Management of Alpha-1 Antitrypsin Deficiency

What Is Alpha-1 Antitrypsin Deficiency?

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Deficiency of alpha-1 antitrypsin (AAT) protein is a genetic disorder predisposing individuals to the development of early-onset pulmonary disease, most commonly emphysema. AAT protects pulmonary tissue from damage caused by neutrophil elastase, an enzyme mobilized in response to infection and inflammation. In individuals with AAT deficiency, a structural defect in the AAT protein results in AAT levels in the lungs that are insufficient to provide adequate protection against damaging enzymes. Lung disease associated with AAT deficiency may present as shortness of breath, wheezing, cough, high sputum production, and frequent lower respiratory tract infections. In the liver, AAT deficiency may manifest as neonatal hepatitis or, in adults, as cirrhosis.

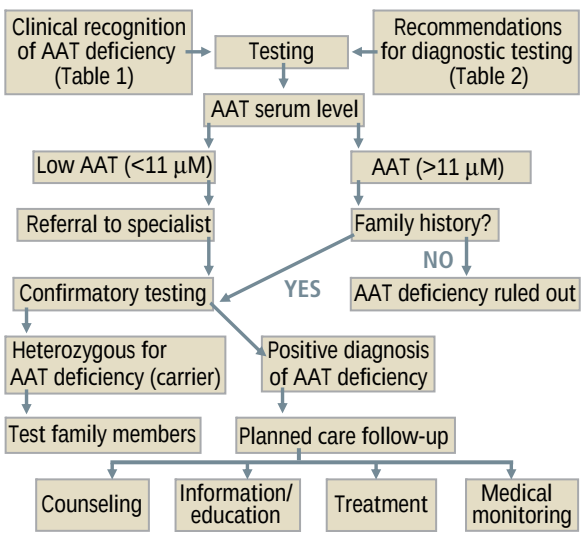
AAT Deficiency Is Widely Underrecognized

AAT deficiency is not a rare disorder but there is little appreciation of its frequency. In fact, AAT deficiency is one of the most common genetic conditions worldwide, occurring with a prevalence similar to that of cystic fibrosis.[1,2] In the United States, it has been estimated that approximately 100,000 individuals could be affected[2] and that 1% to 3% of all chronic obstructive pulmonary disease (COPD) cases may be attributable to AAT deficiency.[3] Despite this, only approximately 5% of individuals receive a correct diagnosis.[3] Large outcomes studies have determined that even in those individuals who receive a positive diagnosis, there are substantial delays from symptom onset to the correct identification of AAT deficiency.[3,4]

Why Are Rates of Diagnosis So Low?

The condition often manifests as insidious symptoms that are commonly confused with those of other respiratory diseases,[5,6] and some individuals may not even have symptomatic lung disease. Moreover, a profound lack of awareness of AAT deficiency exists among both the medical community and affected individuals with respect to the condition itself and to testing for the disease.[7] Finally, a number of obstacles exist in clinical practice that impede prompt diagnosis and effective management.[7] These include time constraints, limited access to appropriate counseling, poor communication both within practices and with external specialists, and pessimistic physician attitudes (therapeutic nihilism and/or the belief that the condition is too costly or complicated to manage).

FIGURE. Diagnosis and Management of AAT Deficiency: An Algorithm for Best Practice Recommendations



Optimal Diagnosis and Management Strategies

The use of best practice recommendations as suggested in the Figure can go some way to surmounting the obstacles noted above.

In the first place, primary care workflow solutions should attempt to incorporate the use of clinical tools that allow practice staff to easily carry out AAT deficiency screening within the time constraints common in a busy office. The development and introduction of patient self-administered questionnaires could be used in this capacity, as has been successfully achieved for screening of COPD.[8]

Table 1 lists features that should prompt the suspicion of AAT deficiency. Recommendations have also been published by the European Respiratory Society and the American Thoracic Society providing clear guidance on which individuals should undergo diagnostic testing for AAT deficiency (Table 2).[2]

TABLE 1. Clinical Recognition of AAT Deficiency

Features that should prompt suspicion of AAT deficiency:

1. Early-onset emphysema regardless of smoking history, or emphysema at any age in the absence of a recognized risk factor
2. Emphysema with worse disease at the base of the lung (shown by chest X-ray)
3. Family history of breathing problems
4. Bronchiectasis without evident cause

TABLE 2. Recommendations for Diagnostic Testing for AAT Deficiency (ATS/ERS Task Force)[2]

Genetic testing is recommended for:

1. Adults with symptomatic emphysema or COPD
2. Symptomatic adults with asthma that is incompletely reversible despite aggressive treatment with bronchodilators
3. Asymptomatic adults with persistent airflow obstruction on pulmonary function tests and with risk factors (ie, smoking or occupational exposure)
4. Adults with necrotizing panniculitis
5. Siblings of affected individuals
6. Individuals with liver disease of unknown etiology

ATS=American Thoracic Society; COPD=chronic obstructive pulmonary disease; ERS=European Respiratory Society.

Once the condition is suspected, diagnostic testing should be initiated, and this usually involves assessment of serum AAT levels. Test kits using dried blood spots collected on filter paper are available free of charge and are sent to an academic research laboratory by regular mail for analysis. If testing reveals a serum AAT level below a protective threshold of 11 µM,[2] then the individual should be referred to a pulmonary specialist for further confirmatory testing, as it is likely that the individual has AAT deficiency. In individuals found to have serum AAT levels >11 µM, a detailed family history should be obtained. When there is no evidence of a family history of AAT deficiency, the condition can effectively be ruled out and the individual should be re-evaluated for another cause of his or her symptoms. Alternatively, if there is a family history, then confirmatory testing is required. Confirmatory testing involves genotyping (by polymerase chain reaction or DNA sequencing), phenotyping (by gel electrophoresis), pulmonary function tests, liver function tests, or computed tomography scan. Genetic testing will also determine whether an individual is heterozygous (a carrier) for the disease, in which case additional family members should also be tested for AAT deficiency following the same algorithm.

Upon receiving a positive diagnosis, the individual enters a planned care follow-up model according to the recommended approach, which involves a series of physician- and specialist-led activities. Since a positive diagnosis brings with it a number of challenges—both medical and social—to individuals and family members, they should be offered counseling (including genetic counseling) that will advise them on the implications of having AAT deficiency and how to reduce their risks for developing any associated health problems that may worsen their prognosis (eg, avoidance of smoking and passive smoking, environmental pollutants, and infection). Affected individuals should also be placed in touch with relevant organizations that will provide information and education.[9-11]

A program of effective treatment should be agreed on, as prompt management of the condition will limit the progressive decline in lung function associated with AAT deficiency and increase quality-adjusted life-years. Treatments may include antibiotic therapy for respiratory infections, pulmonary rehabilitation (recommended for all COPD patients with forced expiratory volume in 1 second [FEV_1] below 80% of predicted value),[12] general treatments for emphysema and COPD (including inhaled bronchodilators and corticosteroids),[12] and specific therapy for AAT deficiency.[2] Augmentation therapy (intravenous purified AAT) is recommended in individuals with airflow obstruction due to AAT deficiency in whom it has been shown to increase lung levels of AAT and slow the rate of lung function decline[13-16]; it may also reduce the associated loss of lung tissue.[17,18] Finally, individuals should be closely monitored by their medical team to receive regular health examinations and spirometry, and to assess adherence to prescribed medications and treatments.

"It is very difficult in the busy primary care practice to implement workflow solutions that raise awareness of AAT deficiency as a possible cause for common respiratory complaints. Once we have a care model in place using easily available tools to recognize and test for AAT deficiency, we can dramatically improve diagnosis and treatment of this disease."
—Leonard Fromer, MD

References

1. Blanco I, de Serres FJ, Fernandez-Bustillo E, et al. *Eur Respir J*. 2006;27:77-84.
2. American Thoracic Society/European Respiratory Society. *Am J Respir Crit Care Med*. 2003;168:818-900.
3. Campos MA, Wanner A, Zhang G, et al. *Chest*. 2005;128:1179-1186.
4. Stoller JK, Sandhaus RA, Turino G, et al. *Chest*. 2005;128:1989-1994.
5. Needham M, Stockley RA. *Thorax*. 2004;59:441-445.
6. Luisetti M, Seersholm N. *Thorax*. 2004;59:164-169.
7. Stoller JK, Fromer L, Brantly M, et al. *Cleve Clin J Med*. 2007;74:869-874.
8. Martinez FJ, Raczek AE, Seifer FD, et al. *COPD*. 2008;5:85-95.
9. The Alpha-1 Foundation. Available at: www.alphaone.org. Accessed Feb 11, 2009.
10. The Alpha-1 Association. Available at: www.alpha1.org. Accessed Feb 11, 2009.
11. AlphaNet. Available at: www.alphanet.org. Accessed Feb 11, 2009.
12. Global Initiative for Chronic Obstructive Lung Disease. Available at: www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed Feb 9, 2009.
13. Wewers MD, Casolaro MA, Sellers SE, et al. *N Engl J Med*. 1987;316:1055-1062.
14. Seersholm N, Wencker M, Banik N, et al. *Eur Respir J*. 1997;10:2260-2263.
15. Wencker M, Banik N, Buhl R, et al. *Eur Respir J*. 1998;11:428-433.
16. The Alpha-1 Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med*. 1998;158:49-59.
17. Dirksen A, Dijkman JH, Madsen F, et al. *Am J Respir Crit Care Med*. 1999;160:1468-1472.
18. Dirksen A, Piitulainen E, Parr DG, et al. *Eur Respir J*. Feb 5, 2009. E-pub ahead of print.

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