

Clinical Allergy Tips

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From the Editor: Due to the fact that the immune system is not restricted by anatomy, Allergy-Immunology Specialists are accustomed to lumping together signs and symptoms from different organ systems. This vignette starts off as an urticaria referral and then takes several twists and turns before resolution. Currently, no specialty has been successful at motivating its physicians to make it a priority to screen for alpha-1 antitrypsin deficiency. There is no reason why Allergy-Immunology Specialists cannot take the lead in the recognition and treatment of this disease.



Think Alpha-1 Antitrypsin Deficiency

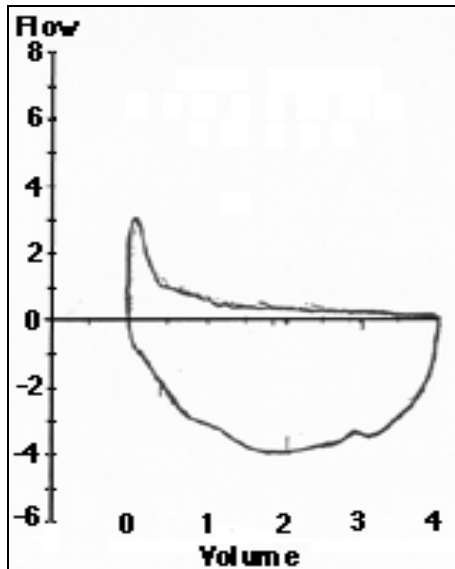
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Alpha-1 antitrypsin deficiency (Alpha-1) is suspected in over 70,000 people in the USA, and prevalence in certain parts of Europe is higher. Unfortunately, only about 10% of cases are diagnosed and the failure to recognize and start augmentation leads to increase in morbidity and suspected earlier onset in mortality. The workup in most cases is simple and obtaining alpha-1 antitrypsin protein levels and genotype usually is an adequate screening test to exclude the disease. However, as noted in the case below, caution is sometimes necessary; and when findings and results conflict, further investigation is necessary.

Who should you screen? The consensus is that all COPD patients, but especially those with early onset disease (before 45) and those with a minimal smoking history, should be screened. Also to be screened are patients with atypical asthma or asthma that does not completely reverse, patients with unexplained panniculitis, bronchiectasis or liver disease – especially if

both the liver and lungs are involved – and lastly C-ANCA positive vasculitis.¹

Margaret is a 40 year-old female referred to us for an evaluation of urticaria. Her urticaria was atypical by history and composed of plaque-like erythematous raised lesions which are often painful and persist and have an increase in temperature. On her exam she was noted to be wheezing and spirometry revealed an FEV-1 of 40% predicted with an obstructive ratio. When questioned about these findings she reported a 10 pack year history of tobacco abuse, but that she had quit 15 years ago. She was told by a pulmonary doctor she had Alpha-1, but not enough that required therapy. Results of a skin biopsy performed on a later appointment were consistent with panniculitis. Her liver function studies were normal. Her alpha level was 78 mg/dl and genotyping revealed MM. CXR and CT of the lungs were consistent with emphysema especially of the lower lobes.



- Does it make sense that Margaret is MM and her alpha level is below normal?
- Does she need additional testing?
- Are patients misdiagnosed by genotyping?
- Should she receive augmentation?

Margaret's serum level is low and she should be expected to have an abnormal allele, yet she is MM, which is normal. At this serum level she should not be at high risk of COPD, but she is young, with minimal tobacco use and has moderate obstructed lung disease.

If you knew that the technique for genotyping only assessed for S and Z alleles and if neither was found, the report would state that the genotype was MM, would you be concerned?

Phenotyping was done and Margaret had an f allele reported. F phenotypes have normal levels of protein but with defective function and Margaret's levels are low. As it turns out Margaret is an f/null with both defective and low protein levels. It is estimated that approximately 2% of cases will have discordant results when testing for alpha deficiency.²

- Would Margaret develop liver disease?
- Should she receive augmentation?
- Does augmentation therapy with Alpha-1 antitrypsin protein replacement work for emphysema and panniculitis?
- If Margaret was a ZZ would augmentation help her liver disease?

Margaret would not be expected to have liver disease and Margaret's LFTs were normal. ZZ patients are unable to secrete alpha and develop liver damage secondary to accumulation of the protein in the liver. Replacement therapy does not improve liver disease. Margaret was placed on alpha augmentation. Her panniculitis improved, and we hope that augmentation therapy will slow the deterioration of her lung function. She was replaced with 60 mg/kg of human Alpha-1 inhibitor IV weekly.^{3,4}

Your last question should be: Why do people have this genetic induced protein deficiency?

Before the antibiotic era, having a very robust inflammatory response to a bacterial pneumonia may have decreased the risk of death associated with pneumonia, even though lung damage could occur and lead to early onset emphysema. In past times with death occurring earlier in age, rarely did the emphysema matter, nor did it affect reproduction. Now that we live longer and have time to develop symptomatic emphysema and have antibiotics so we are not as dependent on mounting a robust inflammatory response, the gene abnormality is no longer beneficial. Thus in this day and age the deficiency provides little benefit and instead causes morbidity and earlier mortality.

References

1. ATS/ERS Standards for the diagnosis and management of individuals with Alpha-1-antitrypsin Deficiency. *Am J Respir Crit Care Med* 2003; 168: 820-823
2. Snyder M, Katzmann J, Thibodeau S, et al. Diagnosis of Alpha-1-Antitrypsin Deficiency: an algorithm of quantification, genotyping and phenotyping. *Clinical Chemistry* 2006; 52; 2236-42
3. Chapman K, Stockley R, Navickis R, et al. Augmentation therapy for Alpha-antitrypsin deficiency: a meta-analysis. *J of Chronic Pulmonary Disease* 2009; 6; 177-84
4. Wencker M, Fuhrmann B, Banik N, et al. Longitudinal follow-up of patients with Alpha-1-Protease Inhibitor Deficiency before and during therapy with IV alpha Protease Inhibitor. *Chest* 2001; 119; 737-744