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Alpha-1 Deficiency: Better Detection May Improve Outcomes for COPD Patients

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ALPHA-1 DEFICIENCY: BETTER DETECTION MAY IMPROVE OUTCOMES FOR COPD PATIENTS

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder that results in debilitating illnesses like: emphysema, COPD, liver disease, and panniculitis. **AATD is highly under-diagnosed based on epidemiologic and population studies that suggest that fewer than 10% of the 60,000-100,000 individuals in the U.S. suspected to have severely deficient alleles have been identified** (Rahaghi et al., 2012). This study examines strategies aimed at improving detection of AATD. The findings indicate that utilizing flags to alert providers of the need for AATD testing initiated by RTs or automated within EMR systems are effective strategies for increasing testing rates and potentially improving detection of emphysema and COPD secondary to AATD therefore eliminating diagnostic delays and improving prognosis for those affected.

Introduction

Alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant condition resulting in decreased or absent levels of alpha-1 antitrypsin (AAT) which is a protease produced in the liver. This allows the uninhibited proteolytic action of neutrophil elastase to overtake the lungs resulting in degradation of lung tissue and early onset (prior to the fourth or fifth decade) emphysema and chronic obstructive pulmonary disease (COPD) (Hatipoglu, Umur & Stoller, 2016). Exposure to environmental pollutants and cigarette smoke greatly increase neutrophil elastase activity and therefore exacerbate lung destruction in AATD individuals. It is thought that similar inflammatory reactions occur in the skin resulting in vasculitis and panniculitis. In addition, intrahepatic accumulation of the defective protein may cause cirrhosis or primary liver carcinoma. This condition accounts for 2%-5% of chronic obstructive pulmonary disease cases in America (Diaz,J.A, Minami, 2017) and is thought to be most common in individuals of Northern European decent (Hatipoglu, Umur & Stoller, 2016).

Statement of the Problem

Despite guidelines from the American Thoracic Society and the European Respiratory Society regarding testing for AATD, the disorder remains highly under-diagnosed. Furthermore, individuals report long delay times (averaging 5-7years) and visits to multiple providers between onset of symptoms and diagnosis which delays opportunities for lifestyle modifications and potential treatment with augmentation therapy that may improve prognosis(Hatipoglu, Umur & Stoller, 2016).

Research Questions

- **What are the barriers to detection of AATD?**
- **Are there effective strategies that may be implemented to overcome barriers to recognition and decrease diagnostic delays allowing for interventions that may decrease progressive loss of lung function in COPD patients with AATD?**

Literature Review

A search of peer reviewed journal articles was performed utilizing electronic databases including: PubMed, Cochrane, and Clinical Key. Several articles published between 2002 and 2017 were retrieved and reviewed including those regarding the pathophysiology and prevalence of alpha-1 deficiency, guidelines for testing and management of patients with AATD, current and emergent therapies for AATD, barriers to diagnosis, and strategies for improved diagnosis. One systematic review of articles published between January 2002 and December 2014 regarding practice guidelines for diagnosis and management of AATD patients was reviewed. An observational study published in 2010 that analyzed barriers to detection by assessing the level of knowledge of AATD among internal medicine house officers and respiratory therapists was included. Three observational studies published between 2009 and 2014 aimed at analyzing processes for improving detection of alpha-1 antitrypsin deficiency were included. Information was also obtained from the Alpha-1 Foundation website and personal interviews with Ronald Reilkoff, M.D. (University of Minnesota Pulmonary, Allergy, Critical Care & Sleep Medicine) and Mary Davis (Sales Director, Grifols USA).

Discussion

Potential Barriers to Detection of AATD:

- Lack of knowledge regarding Alpha-1 among providers and patients.
- Perception among providers that treatment is ineffective.
- Patient fear that diagnosis will affect their ability to obtain life or health insurance or fear of emotional impact.
- Cost associated with testing.

Addressing the Barriers and Exploring Strategies to Overcome Them:

Knowledge of AATD

Taliercio, Chatburn, and Stoller, 2010, conducted a study assessing the knowledge of AATD among internal medicine house officers and respiratory therapists (RTs) at the Cleveland Clinic. There was no statistically significant difference between the physician and RTs mean scores of 54% and 52%, P= .25. **Half of physician scores were below 55% with that being the median for the group. The median for RTs was 50%. Those who rated themselves as "somewhat knowledgeable" on self-assessment scored highest with physician scores of 60% correct and RT scores of 56%, P= < .001**. Physician scores did not change based on post-graduate education level (P= .94), but RTs with 4-year degrees had a higher mean score than those graduating from 2 year programs (56% vs 50%) (Taliercio, Chatburn, & Stoller, 2010).

❑ **Effectiveness of Augmentation with Human Plasma Derived Alpha-1 Protein**

The American Thoracic Society currently recommends augmentation therapy with Alpha-1 antitrypsin derived from human plasma for mild to moderate COPD (FEV_1 of 35%-65%) and alpha-1 antitrypsin deficiency. Despite early randomized control trials that failed to prove improvement in lung function of AATD individuals receiving augmentation therapy while using spirometry and FEV1 as measures, more recent studies have noted reductions in the loss of lung density when subjects were assessed with Computed Tomography rather than spirometry. In addition, observational benefits such as: decreased mortality, reduction of inflammatory markers in sputum, and reduced rates of respiratory tract infections have been noted in those who received augmentation compared to those who did not. The FDA has approved augmentation therapy for mild to moderate COPD due to AATD on the basis of biochemical efficacy, which is described as the ability to raise serum levels to the established protective threshold of 11µM or 57mg/dL (Hatipoglu, Umur & Stoller, 2016).

❑ **Utilizing Respiratory Therapists and Automated EMR algorithms to flag patients for testing:**

Rahaghi et al. (2009) analyzed the effects of a physician alert for AATD testing generated by respiratory therapists following abnormal PFT results. **During the pre-alert period, 6% of included patients underwent testing for AATD compared to 13% in the physician alert phase (p=0.04).** In 2011,Jain, McCarthy, Xu, and Stoller conducted a similar study at the Cleveland Clinic in Ohio utilizing an EMR based flag for testing. The study included 979 subjects during a pre-alert period. 4.7% were referred for testing resulting in 8.9% found to have AATD based on serum levels. Phenotyping of those with low serum levels, resulted in 3.2% with genotype PI ZZ. **During the alert period, 624 patients were determined eligible and the rate of testing increased substantially to 15.1%, P < 0.001.** In conclusion, the studies strongly suggested that utilizing respiratory therapists and EMR flags to identify individuals for testing based on PFT results substantially increased rates for testing individuals clinically indicated at risk for AATD (Rahaghi et al., 2009).

❑ **The Genetic Information Nondiscrimination Act (GINA) of 2008 protects those diagnosed with genetic disorders from discrimination when applying for health insurance and employment (NIH, 2013)**

❑ **Overcoming the Cost of Testing and Providing Patient and Provider resources regarding diagnosis and Management of AATD:**

The Alpha-1 Foundation and many of the pharmaceutical manufacturers of augmentation offer free testing kits for evaluation of AAT serum level and genotype using dried blood spot PCR eliminating this barrier. In addition, the Alpha-1 Foundation offers genetic counseling services for those identified with AATD. In addition, the foundation provides and array of educational offerings regarding AATD diagnosis and treatment to clinicians.(Alpha-1 Foundation, n.d.)

Applicability to Clinical Practice

Primary care is often the first point of entry for many patients with obstructive airway diseases making it an ideal environment in which to implement new strategies for improved detection of alpha-1 antitrypsin deficiency. Fromer (2010) proposed the following process maps aimed at improving diagnosis and management of AATD in the primary care setting.

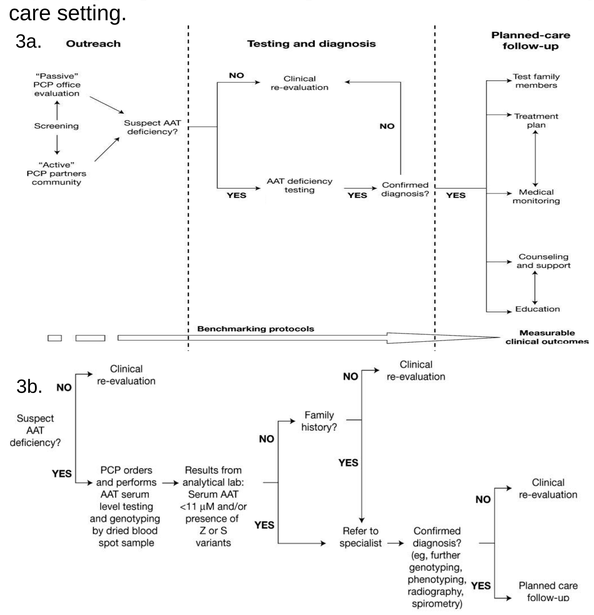

Figure 3a. Proposed process map for AATD screening in the primary care setting
Figure 3b. Proposed diagnosis algorithm for AATD planned care follow-up in the primary care setting.
Image from: Fromer, L. (2010). Improving diagnosis and management of alpha-1 antitrypsin deficiency in primary care: translating knowledge into action. *COPD*, *7*(3), 192–8. https://doi.org/10.3109/15412555.2010.482577

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