EDUCATIONAL COMMENTARY – ALPHA-1 ANTITRYSIN (A1AT) DEFICIENCY

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to

- describe chronic obstructive pulmonary disease.
- define acute-phase protein.
- discuss the laboratory testing used in the diagnosis of α1-antitrypsin deficiency (A1ATD).
- discuss the inheritance of A1ATD.
- discuss the treatment of A1ATD.

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease in which there is inadequate airflow into and out of the lungs. According to the American Lung Association, 12 million cases of COPD are diagnosed in the United States with an additional 12 million cases remaining unrecognized. It is the third leading cause of death. COPD is usually diagnosed in middle-aged or elderly persons. Although the disease is not curable, early treatment can improve symptoms and slow its progression. COPD results when any of the following occur: (1) alveoli, air sacs in the lung, lose their elasticity; (2) alveolar walls are destroyed, thickened, or inflamed; or (3) excess mucus clogs the alveoli. COPD includes 2 major disease processes: emphysema and bronchitis. In most cases of COPD, patients have both emphysema and chronic bronchitis. In emphysema, the walls of the alveoli are damaged, resulting in larger, less elastic air sacs. In chronic bronchitis, inflammation causes the lining of the airways to thicken, and increased production of mucus blocks the airways. The vast majority of cases of COPD are the result of cigarette smoking. Other causes include air pollution and, in rare cases, genetics. The only currently recognized genetic cause of COPD is α1-antitrypsin deficiency (A1ATD). A1ATD was first recognized by Laurell and Erickson in 1963, who found a link in some patients between emphysema and the absence of an α-1 globulin band on serum protein electrophoresis.¹ The Department of Health and Human Services estimates that approximately 100,000 Americans have A1ATD, but many of these cases are improperly diagnosed as asthma.

Alpha-1 antitrypsin (A1AT) is an immune substance classified as an acute-phase reactant (APR). Acute-phase reactants are defined as serum proteins whose concentrations increase or decrease rapidly during inflammation and trauma. To be designated an acute-phase reactant the protein’s concentration must change by at least 25%.² In the inflammatory process, neutrophils are attracted to the site of the trauma or infection. Neutrophils engulf and destroy foreign particles such as bacteria or damaged tissue in a process known as phagocytosis. At the completion of the phagocytic process, the neutrophils release
their contents into the area of inflammation. Among the contents released is an enzyme called neutrophil elastase, which kills bacteria and removes damaged host tissue. However, uncontrolled concentrations of neutrophil elastase destroy the connective tissue (elastin) of the lung. Reduced connective tissue results in increased air spaces, which leads to decreased gas exchange by the alveoli. The outcome is emphysema.

A1AT is an APR that protects the lung tissue from enzymatic destruction by inhibiting the elastase released from neutrophils and macrophages during inflammation. Exposure to cigarette smoke or other respiratory irritants exacerbates the symptoms of emphysema which include shortness of breath, wheezing, and crackles. Not only does the smoke increase inflammation, but it significantly deactivates A1AT, reducing its inhibitory capabilities. Most APRs are produced in the liver in response to cytokines. Cytokines are signaling substances produced during the immune response by monocytes, macrophages, and lymphocytes that allow communication between immune cells. Cytokine production occurs during inflammation that follows infection, tissue injury due to trauma or burns, immunologic disorders, and cancer. The primary cytokine associated with the acute-phase response is IL-6. Other cytokines involved include tumor necrosis factor-α and interferon γ. Acute-phase reactants enhance and/or regulate the inflammatory process. One of the APRs produced in the liver is A1AT; it is also produced to some degree in the epithelial cells of the lungs.

Alpha-1 antitrypsin deficiency is an inherited disease in which there is a defect in the production of A1AT and a reduction in its activity in the lungs. The mutated A1AT is functionally defective as well and is deposited in hepatic cells. Excessive deposits of A1AT can lead to cirrhosis of the liver. The severity of the A1ATD depends on whether the individual has 1 or 2 copies of the affected gene. One alpha-1 gene is inherited from each parent. The M allele is the normal alpha-1 gene and is the most commonly inherited allele of the alpha-1 gene. The Z allele is a variant of the gene and is the most common cause of A1ATD. A person who inherits 2 Z alleles (genotype PiZZ) will have a severe A1ATD (not enough A1AT is produced to protect the lungs from the damage caused by neutrophil elastase). Another cause of A1ATD is the less common variant S allele. Persons with genotype PiSZ will probably develop the disorder but at a later age. Persons who inherit the MZ alleles (genotype PiMZ) or MS alleles (genotype PiMS) are carriers of A1ATD but, in most cases, will produce enough A1AT to protect their own lungs. Environmental factors such as smoking can raise a carrier’s risk for emphysema or other lung disease. A1ATD is most common in Caucasian populations of Europe and North America. The highest frequency of the Z mutation occurs in southern Scandinavia. A1ATD is thought to have originated approximately 2000 years ago in the Vikings and spread across Europe via the Viking raids. The S mutation originated in Portugal.
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There are more than 80 variants of the disease depending on the mutation(s) inherited by the patient. Severe A1ATD causes early-onset emphysema, one of the causes of COPD. A1ATD is the most common genetic cause of liver disease and the most common basis for liver transplant in children. Liver disease will develop in 10% of children with A1ATD.

Cases of A1ATD are commonly misidentified. When symptoms occur, these patients are diagnosed as having COPD or asthma. Testing for A1ATD should be performed in patients with COPD when no other cause has been identified, particularly for those with early-onset emphysema. The criterion standard in diagnostic testing for A1ATD is a combination of genotyping with polymerase chain reaction (PCR) and DNA sequencing and serum assays for A1ATD concentrations. Serum assays use the common technique known as enzyme-linked immunosorbent assay (ELISA). Autoantibodies to elastin may also develop in patients with genotype PiZZ A1ATD. The autoantibodies stimulate the immune response, generating inflammatory processes that further damage the epithelial lining of the lung. Antielastin antibodies can be quantified. Biomarker assays are also being investigated in an effort to determine risk for disease and to provide earlier diagnosis. Earlier diagnosis allows the patient to recognize the need to cease smoking and avoid chemical and environmental exposure to irritants, and for couples to seek genetic counseling before pregnancy.

Treatment for A1ATD follows the protocols used in COPD, which include steroids, antibiotics, breathing treatments, oxygen therapy, and bronchodilators. In addition, patients in some countries are treated with A1AT augmentation therapy, a weekly infusion of A1AT. Although it has been shown that adequate serum levels can be achieved, the efficacy of the treatment remains questionable. Few studies have been performed to assess this aspect of the treatment. Experimental therapy includes gene therapy, stem cell therapy, and other novel approaches.

Significant numbers of A1ATD cases are misdiagnosed. Current laboratory testing and the discovery of appropriate biomarkers should improve the ability to properly diagnose the disease. Early diagnosis and continuing research on new therapies may result in delayed onset of COPD in patients with A1ATD.

References

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