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OPINION ARTICLE

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Pathophysiology of Alpha-1 Antitrypsin Deficiency, its Signs and Symptoms

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Description

A hereditary condition known as alpha-1 antitrypsin deficiency (A1AD or AATD) can cause liver or lung illness. Lung issues often appear between the ages of 20 and 50. Breathing difficulties, wheezing, or a higher risk of lung infections could occur from this. Chronic obstructive pulmonary disease (COPD), cirrhosis, newborn jaundice, or panniculitis are a few possible complications. The *SERPINA1* gene mutation that causes insufficient alpha-1 antitrypsin (A1AT) is the cause of A1AD. Dusts from the environment and cigarette use are risk factors for lung illness. Unblocked neutrophil elastase and an accumulation of aberrant A1AT in the liver are the underlying mechanisms. It is autosomal co-dominant which means that compared to two faulty alleles one likely to cause a milder condition. Based on the symptoms, a diagnosis is suspected, and blood or genetic tests are used to confirm it. Bronchodilators, inhaled steroids, and antibiotics are possible treatments for lung illness. A1AT protein intravenous infusions or, in cases of severe illness, lung transplantation may also be advised. Transplantation of the liver may be an option for those with severe liver disease. Smoking should be avoided. Additionally advised are vaccinations against hepatitis, pneumococcus, and influenza. Those who smoke have a life expectancy of 50 years, compared to almost normal for those who do not smoke.

Pathophysiology

A1AT is a glycoprotein that is primarily produced by hepatocytes in the liver as well as in small amounts by enterocytes, monocytes, and macrophages. It works as an inhibitor of neutrophil elastase a neutral serine protease that regulates lung elastolytic activity and encourages the production of CXCL8 from epithelial cells which maintains the inflammatory state in a healthy lung. Neutrophil elastase can damage elastin and other elements of the alveolar wall of the lung when A1AT is deficient, which may cause emphysema and mucus hypersecretion that may result in chronic bronchitis. Chronic obstructive pulmonary disease (COPD) is made up of both disorders. Alpha-1 antitrypsin levels in normal blood can vary depending on the analytical method but are normally between 1.0 and 2.7 g/L. Blood levels of A1AT in people with the PiSS, PiMZ, and PiSZ genotypes are decreased to between 40% and 60% of normal levels this is typically enough to shield the lungs from the effects of elastase in non-smokers. A1AT levels are less than 15% of normal in PiZZ genotype carriers, and they are more likely to experience panlobular emphysema at a young age. Smoking cigarettes is particularly dangerous for people with A1AD. Cigarette smoke directly inactivates alpha-1 antitrypsin by oxidising crucial methionine residues to sulfoxide forms, which results in a 2,000-fold reduction in the enzyme's activity. This process also increases the inflammatory response in the airways.

Symptoms and Signs

Emphysema, also known as chronic obstructive pulmonary disease, can strike people with A1AD in their thirties or forties even if they have never smoked. However, smoking considerably raises the risk. Wheezing, sputum production, and shortness of breath (during physical exercise and subsequently when at rest) are possible symptoms. The signs and symptoms could resemble asthma or recurrent respiratory infections. A1AD has been linked to a number of liver disease symptoms, such as cirrhosis and reduced liver function. Alpha-1 antitrypsin deficiency in infants can cause early-onset jaundice that lasts a long time. Children with ZZ mutations are 3%–5%

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more likely to experience life-threatening liver illness, including liver failure. The most common cause of infant liver transplants is A1AD. A1AD may result in jaundice, poor feeding, inadequate weight growth, hepatomegaly, and splenomegaly in infants and children. In addition to COPD and chronic liver disease, 1-antitrypsin deficiency has been linked to necrotizing panniculitis (a skin disorder) and granulomatosis with polyangiitis, a condition in which blood vessel inflammation mostly affects the kidneys and lungs.