

ALPHA1 ANTITRYPSIN

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An $\alpha 1$ glycoprotein of molecular weight 50,000 dalton was first isolated in 1955 and was given the name of $\alpha 1$ antitrypsin ($\alpha 1$ AT) after its capacity to link trypsin¹. It is one of the eight protease inhibitors identified in human blood and belongs to the group of “acute phase reactant proteins”, those characterized by a rapid increase in synthesis during acute inflammation² to counterbalance increased proteolytic activity at inflammatory sites thereby preventing tissue destruction³. Galactose, mannose, N. acetyl-glucoseamine and sialic acid comprise 12% of its carbohydrate portion⁴. $\alpha 1$ AT like other plasma proteins is synthesized in the liver and is normally present in blood in concentrations of about 280 mg/100 ml; its concentration can double under various stress conditions like infection, surgery, pregnancy or administration of estrogens⁵. Apart from blood it is also present in many body fluids, having been found in micrograms per milliliter quantities in nasal secretion, tears, saliva, pulmonary secretions, duodenal fluid, cerebrospinal fluid, colostrum and mother’s milk. Its level in normal amniotic fluid is approximately 10% of its normal serum level⁶. The relatively small size of $\alpha 1$ AT allows it to enter a wide variety of body fluids where it is assumed that a broad spectrum protease inhibitor might be useful in counteracting tissue damaging effects of enzymes⁷. $\alpha 1$ AT is a major inhibitor of neutrophil elastase, a destructive enzyme capable of cleaving all of the major connective tissue components of the extracellular matrix of most tissues⁸. The primary site of action of $\alpha 1$ AT is the lower respiratory tract, where it protects the alveolar walls against destruction and hence emphysema⁹. When the serum level of $\alpha 1$ AT is below 80 mg/dl (normal 150-280 mg/dl), as occurs in the hereditary disorder of $\alpha 1$ AT deficiency, there is insufficient $\alpha 1$ AT in the lower respiratory tract to inhibit the burden of elastase and the affected individual develops emphysema^{8,9}. $\alpha 1$ AT deficiency was first described in five patients in Sweden in 1963¹⁰ and it soon became obvious that severe deficiency was familial and highly associated with chronic lung disease, having its onset in the third or fourth decade of life. Individuals having circulating levels of this inhibitor of less than 15% of the normal value are susceptible to the development of familial emphysema at an early age^{11,12}. Role of $\alpha 1$ AT deficiency predisposing to pulmonary emphysema had been universally accepted and even an intermediate deficiency of this protease inhibitor plays a role in the development of the disease¹³. The relationship between intermediate $\alpha 1$ AT deficiency and lung disease is of greater potential significance because of the much larger number of carriers. Its deficiency, possibly allows leukoproteases to go unchecked to attack the lung. In the intermediate deficiency, lung aging proceeds at a slower pace and if uncomplicated, a normal symptom free life span is possible. The addition of cigarette smoking, residence or work in a polluted atmosphere, or repeated chest infections could increase the likelihood of the occurrence of disease by accelerating the tissue destruction¹⁴. An association between $\alpha 1$ AT deficiency and liver disease was first reported in 1969¹⁵. Since then numerous reports of neonatal hepatitis and cirrhosis have appeared. Children with $\alpha 1$ AT deficiency are at an increased risk for the development of liver disease; approximately 10% to 20% of them develop signs and symptoms of liver dysfunction¹⁶. The hepatic disease occurs most often during infancy and may progress to cirrhosis and death¹⁷. Lower values of $\alpha 1$ AT activity were also found in patients with duodenal ulcers¹⁸. Deficiency runs in families probably with an autosomal recessive mode of inheritance¹⁹. Although deficiency is typically associated with either obstructive lung disease or childhood cirrhosis, it has also been reported in association with diverse conditions as chronic pancreatitis, glomerulonephritis and rheumatoid

arthritis²⁰. Serum α 1 AT is inherited via series of codominant alleles which appear to control both the electrophoretic mobility of the α 1 AT and its serum concentration. This P1 (protease inhibitor) system comprises of at least 24 different alleles which can be distinguished by various electrophoretic methods²¹. The alleles have been named alphabetically according to their electrophoretic mobility. An individual with Pi type MM has normal amounts of α 1 AT, their type comprise the vast majority of individuals in most populations. Pi type ZZ is associated with severe α 1 AT deficiency usually associated with familial emphysema or familial infantile cirrhosis and PiSZ heterozygotes have α 1 AT levels approximately 30% to 40% of piM levels and appear to have an increased risk of developing lung or liver disease⁷. Recognizing deficiency phenotypes is clinically important because early diagnosis will allow the patient to avoid exposure to environmental factors that may aggravate lung damage²², thereby improving the patient's life expectancy.

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