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Alpha-1-Antitrypsin Deficiency

Alpha-1 antitrypsin (A1AT) is a glycoprotein which is largely produced in the liver. It is a serine protease inhibitor. Its main function is to balance the action of neutrophil-protease enzymes in the lungs - eg, neutrophil elastase produced by neutrophils in the presence of inflammation, infection or smoking.

If there is a deficiency of A1AT then elastase can break down elastin unchecked; in the lungs this can lead to the destruction of alveolar walls and emphysematous change.

A1AT deficiency is an inherited condition. In those with A1AT deficiency, the protein is still produced but the genetic defect means that the A1AT molecule configuration is changed. As a result, it cannot pass out of the liver into the bloodstream and so cannot pass to the lungs and the rest of the body. Some people with A1AT deficiency develop liver disease. This results from the congestion of A1AT in the liver cells, leading to cell destruction.^[1]

Serum concentration of A1AT below 15-20% of normal is very suggestive of homozygous A1AT deficiency.^[2]

Genetics

There is a mutation in the SERPINA1 gene (previously known as the Pi gene) on chromosome 14.^[3] Over 100 different allelic variants of the A1AT gene have been described. M alleles are the normal variants of the gene. Other common variants are S and Z.

As a result of these different allelic variants, over 20 different variants of the A1AT molecule have been identified, all inherited as co-dominant alleles. Humans have two copies of the A1AT gene and can be homozygous or heterozygous.

Someone who is homozygous MM, will produce normal amounts of A1AT. Common genotypes for people with A1AT deficiency are SS, ZZ, MS, MZ, SZ. However, not everyone with A1AT deficiency develops clinically significant disease. The different genotypes will lead to different serum levels of A1AT. It is the serum level of A1AT that will determine the likelihood of developing clinically significant disease. Most patients with clinical disease are homozygous SS or ZZ. They have the lowest serum levels of A1AT.

A heterozygote MS or MZ will be a carrier of the disease. They produce lower than normal levels of A1AT (around 35% of normal). Evidence has shown an increased risk of liver and lung disease for people who are heterozygous for A1AT deficiency. Studies have shown that A1AT heterozygosity can be an important co-factor in the aetiology of chronic liver disease and a modifier for hepatitis C virus, end-stage liver disease, cirrhosis and hepatocellular carcinoma.^[4]

Epidemiology

- A1AT deficiency is one of the most common inherited disorders among white people.
- North-western Europeans are most likely to carry a mutant A1AT gene.^[1]
- It is estimated that 1 person in 3,000-5,000 has A1AT deficiency.^[5]
- It is a condition that is markedly under-diagnosed which probably relates to the fact that even some people with very low levels of the protein may not exhibit problems. Furthermore, manifestation of the disease is a mixture of genetic predisposition and environmental factors.^[6] For example, a person who is heterozygous may simply have a predisposition to chronic obstructive pulmonary disease (COPD) if they smoke.
- Up to 5% of people diagnosed with COPD are thought to have A1AT deficiency.^[5]

A1AT deficiency is an under-recognised disease which should be considered in any young patient presenting with COPD or in any patient with severe, aggressive COPD.

Presentation

The organs most commonly involved are the lungs and the liver.

Lung disease

- Lung disease does not usually present until people are in their 30s and 40s.
- Smokers tend to develop symptoms around 10 years earlier than non-smokers.
- The symptoms are similar to COPD. The most common presentation is early-onset (when aged in 30s and 40s) emphysema, with the lung bases most affected. However, diffuse or upper lobe emphysema and bronchiectasis can occur. The most common presenting symptoms include dyspnoea, wheezing and cough.^[5]
- Lung cancer has also been reported but it is difficult to ascertain causal association due to other environmental factors.^[7]

Liver disease

- Not everyone with A1AT deficiency will develop liver disease.
- Neonates with A1AT deficiency may present with neonatal jaundice and hepatitis; older children may develop hepatitis, cirrhosis and liver failure due to A1AT deficiency.
- Many adults with A1AT deficiency will show some signs of abnormalities in LFTs but, in some, the build-up of A1AT in the liver can lead to hepatitis, fibrosis, cirrhosis and liver failure. With cirrhosis there is a risk of hepatocellular carcinoma.

Investigations

- Serum levels of A1AT can be measured.
- Phenotyping can be carried out on those with low serum levels.
- CXR and lung function testing (even in the absence of symptoms). Consider high-resolution CT scanning of the chest.
- LFTs and possibly liver biopsy.

Family members of an index case should also be investigated.

Management

A1AT deficiency without symptoms

- Where the diagnosis is made in the absence of symptoms there should be advice about not smoking and referral to a chest clinic for the assessment of possible occult disease.
- Many advise restraint with regard to alcohol consumption. However, one study suggests that neither alcohol nor viral hepatitis predisposes to advanced liver disease; however, two factors that do are obesity and being male.^[8]

Lung disease

- COPD is managed as per non-A1AT deficiency COPD cases - ie cessation of smoking, bronchodilators, pulmonary rehabilitation and energetic treatment of infection. See separate [Chronic Obstructive Pulmonary Disease](#) article.
- Lung volume reduction surgery may be helpful in selected patients.
- Lung transplantation may also be considered in appropriate cases.
- Pneumococcal and yearly influenza vaccinations are recommended.

Liver disease

- Liver function should be monitored and liver disease treated as for liver disease and cirrhosis of other causes. See separate [Cirrhosis](#) and [Liver Failure](#) articles.
- Hepatocellular carcinoma screening is also needed (more common in males than in females).
- Liver failure may require transplantation.

Recombinant A1AT therapy

- As the underlying problem is deficiency of circulating A1AT, a logical form of treatment is to replace it. [9]
- Replacement of A1AT effectively elevates circulating levels but the cost-effectiveness and clinical effect are still not ascertained. [1, 10]
- A1AT augmentation therapy has been recommended by some authorities, particularly for non-smoking or ex-smoking patients with COPD attributable to emphysema and documented A1AT deficiency who are receiving optimal pharmacological and nonpharmacological therapies. [11]
- A Cochrane review concluded that augmentation therapy with A1AT could not be recommended, in view of the lack of evidence of clinical benefit and the cost of treatment. [10]
- In the UK, National Institute for Health and Care Excellence (NICE) guidance does not recommend the use of augmentation therapy in A1AT deficiency at present. [12]

Gene therapy

Gene therapy for A1AT deficiency is being investigated and may be a treatment option in the future. [9]

Prognosis

The prognosis is very variable. Those people who are diagnosed with A1AT deficiency after screening (so before they develop any symptoms) tend to have a better prognosis than those who are diagnosed after symptoms have already developed. A worse prognosis is associated with a more severe degree of airflow obstruction. People who smoke are more seriously affected and have a greater risk of dying from the disease. [10]

Further reading & references

- [British Liver Trust](#)
 - [Children's Liver Disease Foundation](#)
1. Kaplan A, Cosentino L; Alpha1-antitrypsin deficiency: forgotten etiology. *Can Fam Physician*. 2010 Jan;56(1):19-24.
 2. McElvaney NG; Diagnosing alpha1-antitrypsin deficiency: how to improve the current algorithm. *Eur Respir Rev*. 2015 Mar;24(135):52-7. doi: 10.1183/09059180.10010814.
 3. Alpha-1-Antitrypsin Deficiency; Online Mendelian Inheritance in Man (OMIM)
 4. Kok KF, Wahab PJ, Houwen RH, et al; Heterozygous alpha-1 antitrypsin deficiency as a co-factor in the development of chronic liver disease: a review. *Neth J Med*. 2007 May;65(5):160-6.
 5. Brode SK, Ling SC, Chapman KR; Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease. *CMAJ*. 2012 Sep 4;184(12):1365-71. doi: 10.1503/cmaj.111749. Epub 2012 Jul 3.
 6. DeMeo DL, Silverman EK; Alpha1-antitrypsin deficiency. 2: genetic aspects of alpha(1)-antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. *Thorax*. 2004 Mar;59(3):259-64.
 7. Yang P, Bamlet WR, Sun Z, et al; Alpha1-antitrypsin and neutrophil elastase imbalance and lung cancer risk. *Chest*. 2005 Jul;128(1):445-52.
 8. Bowlus CL, Willner I, Zern MA, et al; Factors associated with advanced liver disease in adults with alpha1-antitrypsin deficiency. *Clin Gastroenterol Hepatol*. 2005 Apr;3(4):390-6.
 9. Chotimall SH, Al-Alawi M, McEnery T, et al; Alpha-1 proteinase inhibitors for the treatment of alpha-1 antitrypsin deficiency: safety, tolerability, and patient outcomes. *Ther Clin Risk Manag*. 2015 Jan 29;11:143-51. doi: 10.2147/TCRMS51474. eCollection 2015.
 10. Gotzsche PC, Johansen HK; Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. *Cochrane Database Syst Rev*. 2010 Jul 7;(7):CD007851.
 11. Marciniuk DD, Hernandez P, Balter M, et al; Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. *Can Respir J*. 2012 Mar-Apr;19(2):109-16.
 12. [Chronic obstructive pulmonary disease](#); NICE Clinical Guideline (June 2010)

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