Alpha-1 antitrypsin fact sheet for Primary Care

What is Alpha-1 antitrypsin?

Alpha-1 antitrypsin (AAT) is a protease inhibitor produced in the liver and transported to the lungs where it may also be produced locally by macrophages and bronchial epithelial cells. AAT protects the respiratory tract from enzymes released from white cells as part of normal immune function.

What is AAT deficiency?

Individuals with AAT deficiency have lower effective concentrations of AAT in their blood. Genetic changes (polymorphisms) can produce AAT that does not work properly (dysfunctional allele), AAT that is produced but becomes trapped or degraded intracellularly (deficiency alleles), or rarely a complete absence of AAT protein (null allele). Some polymorphisms can result in AAT that is both deficient and dysfunctional.

The effects of AAT deficiency are varied and, at least in part, depend on the type of polymorphism(s) present in an individual. Some people will suffer no ill effects whatsoever. The common clinical consequence of AAT deficiency is an increased risk of emphysema due to cumulative damage to the lungs by neutrophil elastases. Some patients may be at increased risk of liver disease including cirrhosis.

How common is AAT deficiency?

Approximately 1 in 3000 people in the UK have AAT deficiency; around 1 in 25 northern Europeans are carriers for AAT deficiency.

How is AAT deficiency diagnosed?

The concentration of AAT can be directly measured in blood (serum sample). If it is found to be low then the lab will go on to do phenotyping studies to establish whether there is a deficiency variant present.

Occasionally, a low concentration of AAT may be picked up when serum electrophoresis is requested due to a reduced alpha zone. Direct measurement of AAT and phenotyping may then be performed to confirm this finding.

It should be noted that AAT is an acute phase reactant and therefore even patients with AAT deficiency may have normal or high levels of AAT during acute infection/inflammation. If acute infection or inflammation is suspected then a CRP should be requested at the same time. If CRP is raised then AAT should be repeated when the patient is well.

When should AAT be requested in primary care?

AAT is part of the non-invasive liver screen. It should also be considered in early-onset emphysema or emphysema in the absence of any risk factors (e.g. smoking, occupational dust exposure etc.) or where there is a strong family history of lung or liver disease.

What do the phenotyping results mean?

There are > 100 AAT variants, however, only a handful have the potential to cause AAT deficiency. The two most common AAT deficiency alleles are S and Z; the normal AAT allele is known as M. Individuals with the S allele have ~ 80% of normal circulating AAT due to intracellular degradation. This level of AAT is usually sufficient to protect the lungs but additional stressors e.g. smoking or environmental factors may increase the risk of emphysema in homozygotes. Patients with one S allele and one normal M allele generally have enough circulating AAT to provide adequate protection to the lungs.

The Z allele causes AAT to become trapped in the hepatocytes resulting in circulating levels ~15% of normal, however, AAT that does reach the circulation is dysfunctional and less effective. Patients with two copies of the Z allele are at risk of early onset emphysema due to inadequate protection for the lungs. In addition, AAT trapped in the hepatocytes directly causes liver injury which may range from mild hepatitis to cirrhosis requiring transplant. Individuals with one Z allele and one normal M allele are at a slightly increased risk of emphysema or liver disease. Individuals with one S allele and one Z allele have a moderate risk of emphysema and a slight increased risk of liver disease.

Normal AAT phenotypes are reported as M* rather than MM as it is not possible to exclude the presence of a null allele. However, this would be a very rare occurrence and would usually be associated with a much lower than expected AAT concentration. Individuals with a null allele are not at risk of liver disease.

Phenotype	[AAT] 95% Range (g/L)*	Risk of Emphysema	Risk of liver disease
M/M	1.0-2.73	No increased risk	No increased risk
M/S	0.84-2.25	No increased risk	No increased risk
M/Z	0.61-1.56	Slight increased risk	Slight increased risk
M/Null	0.47 – 1.3	Possible slight increased risk	No increased risk
S/S	0.49-1.81	Possible slight increased risk	No increased risk
S/Z	0.42-1.08	Moderate risk (20-50%)	Slight increased risk
Z/Z	0.15-0.57	High risk (80-100%)	High risk
Null	0	High risk	No increased risk

*It should be noted that AAT is an acute phase reactant and therefore levels may be higher than expected during acute infection/inflammation regardless of phenotype.

What advice should be given to patients with AAT deficiency?

Individuals with existing emphysema or liver disease identified as having AAT deficiency should be offered a referral to a specialist for advice and management as should those with a ZZ or SZ phenotype.

All patients with AAT deficiency should be advised to avoid smoking and dust particles or chemicals that could irritate the lungs. Those with a Z type deficiency (or SZ) should also be advised to moderate alcohol consumption as this may increase the risk of developing liver disease.

Carriers of AAT deficiency alleles are unlikely to develop serious health problems but it is advisable to avoid cigarette smoke as carriers may be slightly more likely to develop lung problems if exposed to smoke.

Should family members be tested?

There are currently no UK guidelines regarding family studies for patients with AAT deficiency. However, joint standards produced by the American Thoracic Society and European Respiratory Society recommended that siblings of individuals with AAT deficiency should also be tested. Testing of other first degree relatives or partners could be considered but is not routinely recommended.

The chances of an individual passing on carrier status or AAT deficiency to their children are shown in the table below.

	Partner Normal	Partner Carrier
Patient with AAT deficiency	All children will be carriers. No children will have AAT deficiency.	For each child there is a 1 in 2 chance that they will be a carrier or have AAT deficiency.
Patient Carrier	For each child there is a 1 in 2 chance that they will be a carrier. No children will have AAT deficiency.	For each child there is a 1 in 2 chance that they will be a carrier. For each child there is a 1 in 4 chance that they will have AAT deficiency.

References

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