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Focus

ALPHA-1 ANTI-TRYPSIN DEFICIENCY

Alpha-1-antitrypsin (A1AT) is a member of the serine protease inhibitor (serpin) superfamily of proteins, which also includes alpha-1 antichymotrypsin, C1 inhibitor, antithrombin and neuroserpin.

It is produced mainly in the liver and reaches the lungs via the circulation, but is also produced locally by macrophages and bronchial epithelial cells. Despite its name, A1AT reacts more avidly with neutrophil elastase than with trypsin, and provides more than 90% of the protection against the action of neutrophil elastase in the lower respiratory tract. This enzyme, amongst others, has been implicated in the pathogenesis of emphysema.

ALPHA-1 ANTI-TRYPSIN DEFICIENCY

Alpha-1 anti-trypsin deficiency (A1ATD) is a relatively common but underdiagnosed genetic condition which predisposes to:

- Chronic obstructive pulmonary disease (COPD)
- Liver disease, especially cirrhosis and hepatocellular carcinoma
- Panniculitis
- Vasculitis.

Genetic epidemiological studies and direct population-based screening have determined a prevalence of approximately 1:4500 in the USA[1-4]. Various studies in Europe have shown prevalences of between 1/5000 and 1/2000 for the most severe form of A1ATD (ZZ genotype, see "Genetics of AATD") and between 1/100 and 1/3 for the mildest form (MS genotype), depending on the population studied. In Ireland, the prevalence of the severe ZZ genotype has been estimated at 1/2104, and of the MS genotype at 1/10, amongst the highest in the world[5].

GENETICS OF A1ATD

A1ATD is inherited as an autosomal codominant condition for which more than 120 alleles have been identified. The responsible gene, SERPINA1, is located on chromosome 14.

Phenotypes and genotypes are classified by a PI (for protease inhibitor) coding system, in which the names of the inherited alleles follow the PI; usually letters to denote the migration of the molecule in an isoelectric pH gradient from "A" for anodal variants to "Z" for slower-migrating variants. For example, PI*MM for individuals homozygous for the normal "M" allele and PI*ZZ for those homozygous for the Z allele. "Phenotype" refers to protein expression as demonstrated by isoelectric focussing, and "genotype" reflects the specific allelic combination (as demonstrated by e.g. allele-specific amplification).

The most common mutations associated with disease are the Z (Glu342Lys) and S (Glu264Val) mutations, caused respectively by single amino acid replacement of glutamic acid at positions 342 and 264 of the polypeptide. "Null" mutations lead to a complete absence of A1AT production. While extremely rare, they are associated with a very high risk of emphysema. The Z mutation allele accounts for about 95% of clinically recognised cases of A1ATD.

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The mutations lead to loss of function due to conformational instability of the β-pleated sheet structure common to serpins.

1. Loss of antiprotease activity, as well as loss of the anti-inflammatory effects of A1ATD, predispose to emphysema.

2. In the case of PI*ZZ A1ATD, polymerisation results in accumulation of aggregates of A1AT in hepatocytes, leading to cirrhosis.

3. Panniculitis may accompany several A1AT phenotypes, including PI*ZZ, PI*SZ, PI*SS and PI*MS. The cause is probably unopposed proteolysis.

4. Several studies have shown an associated with PR3 antibody-positive vasculitis and A1ATD, especially PI*ZZ, ZS and SS. The pathogenesis is poorly understood.

DETECTION AND DIAGNOSIS

A1ATD is an underdiagnosed condition with most cases being mis-diagnosed as COPD or refractory asthma. Because of this, long delays frequently occur between presentation of first symptoms and correct diagnosis[6].

This is particularly unfortunate as effective A1AT replacement therapies are available in many cases, reducing mortality and slowing the decline of FEV1 and the progression of emphysema[7].

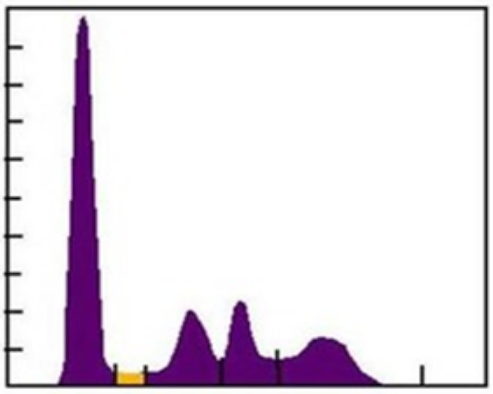
Guidelines produced by the WHO and the American Thoracic Society/European Respiratory Society recommend targeted screening programmes for the detection of A1ATD patients[8,9]. However, as A1ATD is so common in Ireland, an especially high index of suspicion needs to be maintained when considering the differential diagnosis of COPD, emphysema and cirrhosis.

The diagnosis is made by:

1. Determining the serum A1AT level. Homozygous carriers for the Z mutation (PI*ZZ individuals) and compound heterozygotes (PI*SZ individuals) have A1AT levels that are, respectively, 7 - 15% and 30 - 35% of the normal serum A1AT concentrations. Heterozygous carriers of the Z, and homozygous carriers of the S mutation (PI*SS) have A1AT concentrations between 60 and 80% of normal. Null alleles are associated with no detectable circulating A1AT (less than 1% of normal).
2. When serum levels are low (i.e.: less than 0.74 g/L in adult females and 0.81 g/L in adult males), or when there is a family history of A1ATD, genotyping is recommended.

Many clinicians advocate the simultaneous assessment of serum A1AT levels and genotyping.

A1ATD is also diagnosed coincidentally on examination of a serum protein electrophoresis gel or a capillary electrophoresis tracing performed for other reasons. A low level of alpha-1 globulins is noted. Also, the MS phenotype may be detected as an additional band in the alpha-1 zone. In fact, A1ATD was first discovered by Laurell and Eriksson in 1963 by their observation of the absence of the alpha-1 protein band in 5 of 1500 serum protein electrophoresis samples analysed over a 6-month period in Malmö, Sweden[10,11].



Serum protein electrophoresis gel showing a decreased alpha-1 zone due to A1ATD

TEST INFORMATION

Please find details below regarding A1ATD analysis which may be ordered through your local laboratory or directly with Biomnis Ireland

A1AT levels:
Sample Requirements:1 mL serum refrigerated 2 – 8 ° C.
Turnaround time: 5 days
Methodology: Nephelometry.

A1AT genotype:
Sample requirements: 5 mL EDTA whole blood at room temperature.
Turnaround time: 2 weeks
Methodology: PCR-RFLP

CONTACT US

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