Brochure - Alpha-1 Antitrypsin Deficiency (A1AD)

Background

A1AD is a common genetic (inherited) disorder associated with low levels of a natural protein known as alpha-1 antitrypsin (AAT). This disorder leads to decreased AAT activity in the blood and lungs, and in some people, deposits of abnormal AAT in the liver. Low levels of AAT can cause a number of diseases, most commonly in the lungs and liver but sometimes in the skin and blood vessels.

It is thought that people with A1AD can become sick as they don't have adequate AAT to fight infection, control inflammation and protect the lungs or because it can build up in the liver, causing scarring. AAT keeps an enzyme called neutrophil elastase under control so it doesn't attack the body's healthy tissues. Individuals can experience different levels of sickness or may not get sick.

Unfortunately, there is no cure for A1AD and there are limited treatment options, however, clinical trials offer hope for a cure within 10 years. New treatments will minimise the reliance on lung and liver transplants in individuals with severe disease.

Rare or Common

In Australia, approximately one in nine individuals has a deficiency which includes both common and rare forms. A1AD is under-recognised and sometimes misdiagnosed as asthma or COPD. It is thought that less than 10% of cases have been found. (1)

There are over two million people in Australia with some level of A1AD deficiency. S and Z are the most commonly seen deficiencies. It is estimated that there are over 4,000 people with ZZ genotype. About four percent of people have the milder MZ genotype. (2) Some very rare genotypes (e.g. Null) are not well-understood.

A1AD was traditionally considered a disorder inherited from European ancestors. However, recent epidemiological studies have found A1AD in most continents. The Z mutation is thought to have come from the Vikings and the S mutation from the Iberian Peninsula thousands of years ago. (3) Other rare mutations can appear randomly and are named after the town where the oldest person lived, when diagnosed (e.g. $M_{\text{mineral springs}}$). (4)

Genes

Everyone has two alpha-1 antitrypsin (AAT) genes (one passed from mum and one from dad). This means that they are co-dominant genes that both contribute to the AAT levels found in your blood. Which AAT genes you inherent is random, like tossing a coin.

Approximately eleven percent of people (about 1 in 9) in Australia have at least one faulty AAT gene. Faulty AAT genes are sometimes described as a gene mutation, a variant, an abnormal gene or an AAT deficiency (A1AD).

The reason why some people with a deficiency become sick, and others do not, is not well understood. In general, getting lung disease from A1AD is thought to be linked to not having other types of protective genes, being exposed to environmental or occupational triggers (such as pollution), or having an immune trigger (e.g. being sick from something else) which may start the A1AD lung disease process. [5]

Alpha-1 Antitrypsin and its Role in Health and Disease

AAT is a protein which is made mostly in the liver and released into the bloodstream. The main function of AAT is to protect the lungs. If your body doesn't make enough AAT, or if it is destroyed or becomes trapped in your liver i.e. due to its abnormal shape – called "misfolded", you could develop:

- lung disease (e.g. emphysema, bronchitis, bronchiectasis) [6]
- liver problems (e.g. hepatitis, fibrosis, cirrhosis, cancer) [7]
- skin problems (e.g. necrotising panniculitis, psoriasis, angioedema, urticaria)
- blood vessel problems (e.g. vasculitis, aneurysms), problems with the digestive system (e.g. gall stones)
- kidney problems (e.g. IgA nephropathy, [8] proliferative glomerulonephritis).

A1AD is associated (co-occurrence) with a variety of other diseases but further studies are required to prove that A1AD causes other health problems including:

- asthma [9]
- rheumatoid arthritis (no link found)
- diabetes [10]
- arterial hypertension [10]
- chronic kidney disease [10]
- inflammatory bowel disease [11; 10]
- pancreatitis [12]
- autoimmune disease [11]

AAT protects the body from enzymes that are released from inflammatory cells such as white blood cells. White blood cells are important to fight infections and they release an enzyme called neutrophil elastase which helps digest bacteria, damaged and old cells. In people with a severe AAT deficiency, neutrophil elastase can get out of balance and doesn't know when to stop digesting, so it can damage healthy lung tissue. Without enough AAT to protect lung tissue, it can lead to emphysema.

Gene Mutations

- NORMAL AAT GENES
  People who have inherited two normal AAT genes are described as having the MM genotype.

- ONE FAULTY GENE
  If you have one faulty gene (e.g. S or Z) you will be deficient in AAT but are less likely to get disease. However, some individuals with one faulty gene do develop liver, lung and gall bladder disease e.g. MZs.

- FAULTY GENE - Z
  Although the Z allele is considered rare, it is the most common “severe deficiency” protein. [13] If you inherit two Z genes you are referred to as ZZ genotype.

- FAULTY GENE – S
  Another common deficiency is known as the S genotype. When paired with Z, SZs are at risk of lung disease if they smoke.

- RARE GENES - Null
  Rare types of AAT include Null genotypes. Null genotypes may have no detectable AAT protein or it could be dysfunctional and doesn’t form normal AAT. Some types of Nulls are at risk of lung disease.
  Note: More information about rare genes is available in the Alpha-1 Organisation Australia (A1OA) brochure *Issues Associated with Alpha-1 Antitrypsin Deficiency*.

- TWO FAULTY GENES
  If you inherit two faulty genes you are likely to be severely deficient in AAT (e.g. ZNull, ZZ) and have higher risk of disease. If you have ZZ or SZ genotype you are at risk of liver and lung disease. [14] SZ genotype has lower risk of lung disease if they don’t smoke. At least 25% of ZZ adults who have never smoked will develop progressive airflow obstruction.

Testing for A1AD

Testing children at birth for A1AD is not routinely undertaken in Australia. Individuals are usually diagnosed following testing for unexplained symptoms. Testing for A1AD should occur if one or more of the following features exist:

- Early onset emphysema (aged 45 years or younger) / early-onset COPD
- Emphysema that is basilar (mostly at the bottom of the lungs/lung bases)
- A diagnosis of “adult asthma” that doesn’t improve with puffers (inhaled corticosteroids) / or airflow obstruction that is not reversible after aggressive treatment with bronchodilators
- Unexplained liver disease
- A diagnosis of necrotising panniculitis
- A diagnosis with C-ANCA-positive vasculitis
- Unexplained bronchiectasis
- A family history of emphysema, bronchiectasis, liver disease or panniculitis

Testing for Rare Genotypes

In the case of rare alleles (e.g. Null/Bellingham, F/Null) diagnosis can be challenging as standard testing focuses on S and Z mutations. Genetic analysis will be required, especially for rare types of AAT.

Inheritance of A1AD and the Importance of Family Testing

If both parents have one faulty gene, children may inherent one, two, or no faulty genes, based on chance. The chance of developing disease is greater if you have two faulty genes.

Lung Disease in A1AD

Lung disease is the most common problem associated with severe deficiency with up to 45% of ZZ adults dying from emphysema and 5% from other severe lung disease. [15] Sometimes, alphas with lung issues are misdiagnosed with asthma, as it can mimic A1AD lung disease. Smokers are at higher risk of experiencing symptoms of lung disease earlier than non-smokers.

- Genetic emphysema is rarely detected before 30 years of age
- Lung symptoms most commonly show up in adults in their 40s or 50s
- Thirty to forty percent of lung affected individuals with A1AD will have bronchitis [16]
- Approximately 3% of people with a diagnosis of COPD will have A1AD
- At least 50% of lung affected people will have bronchiectasis.

Lung Symptoms

The most common lung related symptoms include:

- shortness of breath (often experienced when walking up a hill)
- rapid heart rate upon standing
- chronic cough and mucus (phlegm/sputum)
- wheezing
- susceptibility to catching viruses even the common cold
- regular chest infections
- difficulty exercising (lower than normal level ability to perform)

Management of Lung Disease

Not many specific lung treatments are available for A1AD, so people are usually treated for COPD. You may be prescribed puffers (inhalers used in asthma) to open up your airways and to help with inflammation and mucus production (e.g. inhaled corticosteroids to reduce airway swelling and mucus production).

Augmentation Therapy

In some countries but not in Australia, standard treatment includes augmentation therapy which has been shown to slow lung decline.

- Augmentation therapy is typically a weekly infusion of AAT.
- Augmentation therapy can be privately purchased, if approved by the Therapeutic Goods Administration (TGA), following an application by your doctor. The purchase price is linked to body weight averaging $100,000 per annum.
- Accessing augmentation therapy through clinical trials (if you meet the trial recruitment guidelines) is possible from time to time. See A1OA's brochure on A1AD clinical trials.

Liver Disease in A1AD

Liver disease can present at any age. Liver damage may come and go, be mild or serious (e.g. cirrhosis). Problems with the liver can include scarring of the liver (i.e. cirrhosis), liver cancer and liver failure.

It is estimated that four to ten percent of children with the severe form of A1AD (e.g. the ZZ genotype) may have liver damage [14] which can show up in the first year of life but most children do not have major liver problems, while some will require a liver transplant. A1AD accounts for 3.51% of paediatric liver transplants but A1AD is the most common genetic cause of liver disease in children. [5]

Accumulation of misfolded Z protein can occur before developing inflammation or fibrosis. [13] Approximately 10-15% of people with Z allele will have clinically significant liver disease in their first 20 years of life. [17]

Liver disease is more common in older adults with ZZ genotype so monitoring by a liver specialist (a hepatologist) and testing is important including regular liver scans, blood tests. Up to 30% of ZZ individuals may develop liver disease in later life. [15]

Liver damage is thought to occur because AAT becomes stuck in the liver, which can lead to the retention of protein polymers, scarring (fibrosis) and cirrhosis of the liver. [14] Children may have liver problems in the first few years of life or later. Most liver problems have been resolved by 18 years of age. [14]

A biopsy may be recommended to see the extent of liver issues. If liver problems emerge treatments may include vitamin supplements, medicine to stop itching or jaundice and treatments for bleeding and fluid built up in your belly.

Liver symptoms

Adults and children may have all or some of these liver related symptoms:

- jaundice
- pale, foul-smelling stools
- dark urine
- itching
- loss of appetite
- no energy / fatigue
- swollen / enlarged abdomen from accumulated fluids (ascites)
- easy bruising
- portal hypertension
- bleeding from the oesophagus or stomach from portal hypertension
- elevated liver enzymes
- liver dysfunction
- enlarged liver (hepatomegaly)
- liver cirrhosis
- swelling of the legs
- drowsiness from a build-up of waste products
- susceptibility to infection in late disease
- hepatitis.

Management of Liver disease

Current management for people with liver disease is supportive care and liver transplantation. There are currently clinical trials underway that aim to stop the production of faulty AAT which can get trapped in the liver.

Autophagy is one therapeutic strategy that is being explored to preserve the liver. Autophagy is a "clearance pathway" and these studies are exploring how to prevent the accumulation of harmful Z-aggregates. It is hoped that a genetic cure will be available in the next ten years.

Skin Disease in A1AD

See the A1OA Fact Sheet *Panniculitis* for information.

Blood Vessel Disease in A1AD

A rare but serious disease called granulomatosis with polyangiitis or Wegener's granulomatosis can cause vasculitis (causing problems with blood vessels). A diagnosis of A1AD vasculitis requires quick medical treatment with drugs to suppress the immune system.

Other Problems

Some adults experience other symptoms that may be associated with A1AD but debate continues as to whether A1AD is a direct cause or an association.

Treating Alpha-1 Antitrypsin Deficiency

If diagnosed with A1AD, adults may be referred to both a lung and liver specialist and have annual monitoring of liver and lungs.

Staying Healthy

Staying healthy is important by:

- having regular check-ups of lungs and liver
- avoiding alcohol
- avoiding cigarette smoke
- have sputum tests (to check for infections that can cause lung damage)
- having regular vaccinations (including hepatitis A and B and pneumonia)
- maintaining a healthy weight
- avoiding metabolic syndrome and fatty liver
- avoiding lung infections and taking antibiotics at the first sign of infections
- attending pulmonary rehabilitation, especially after an exacerbation
- regularly exercising.

More Information

See the A1OA brochure *Issues Associated with Alpha-1 Antitrypsin Deficiency*.

Where to go for information and support

Alpha-1 Organisation Australia: www.a1oa.org.au; email: contactus.a1oa@gmail.com.

Updated July 2020

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