Brochure – Issues Associated with Alpha-1 Antitrypsin Deficiency

Background

This brochure contains information about the genetic disorder known as alpha-1 antitrypsin deficiency (A1AD). A1AD is a disorder, not a disease, but can cause disease in some people. Not everyone with abnormal alpha-1 antitrypsin (AAT) is affected by the deficiency but if you are, your experience and symptoms can be different from someone else with the disorder.

A1AD is a complicated and sometimes challenging diagnosis, affecting approximately one in nine people in Australia, but many individuals remain undiagnosed. The name of the faulty gene is the SERPINA1 gene. The SERPINA1 gene provides instructions for making a protein called alpha-1 antitrypsin (AAT). When normal instructions aren't made, illness associated with A1AD can occur due to a number of reasons including:

- abnormal AAT can build up in the liver, rather than entering the bloodstream to protect the lungs, causing inflammation or scarring in the liver, and damage to the lungs
- individuals don't produce detectable alpha-1 protein (and have a Null diagnosis) so they don't develop liver disease but could have lung problems
- dysfunctional AAT can make normal levels of AAT but dysfunctional AAT can't inhibit damage from neutrophil elastase (a natural enzyme that AAT usually keeps in balance). [1]

The most common problems seen in adults are emphysema and bronchiectasis (sometimes called chronic obstructive pulmonary disease - COPD) and liver disease - (e.g. cirrhosis and / or cancer of the liver cells i.e. hepatoma.) Less common conditions include a skin problem called panniculitis and a blood vessel problem (vasculitis) that causes inflammation of the vessels in your nose, sinuses, throat, lungs and kidneys.

Staying Healthy

If you have received a diagnosis of A1AD:

- maintain a healthy weight
- eat a healthy diet e.g. Mediterranean diet, minimise the amount of carbohydrates which helps breathing
- get regular exercise and participate in pulmonary rehabilitation if lung affected
- avoid lung irritants including cigarette smoke, gas, dust, environmental and household chemicals which can damage your lungs
- wear a face mask when near people, to avoid lung infections
- stay away from sick people who have a cold or a chest infection
- take antibiotics as soon as diagnosed with a lung infection
- get an annual flu vaccine
- get vaccinated against pneumonia
- minimise your alcohol intake

Gene Related Issues

Alpha-1 Antitrypsin (AAT)

If you inherit one or two faulty genes you have lower than normal levels of AAT. You can suffer from inflammation, [2] infection and damage, as AAT helps the body's immune response. [3; 4]

In general terms, the lower the level of AAT, the higher the risk of illness. It is not well understood why some people develop diseases and others do not, including some people with a severe deficiency (e.g. ZZ), who may lead a normal life.

AAT is an acute phase protein which means it changes its serum concentration in response to inflammatory cytokines. This explains some variation in AAT blood levels. [5] However, repeat tests usually aren't required.

AAT is affected (reduced) by obesity, smoke, high glucose levels and bacterial proteases. [6]

Table 1: Common Genotypes and Example Lab Range of AAT found in the Blood

Genotype	Range shown in g/L
MM (two normal genes)	1.00 – 3.50
MZ (one normal, one severely deficient gene)	0.74 – 2.10
SS (two deficient genes)	1.00 – 2.00
SZ (one deficient, one severely deficient gene)	0.75 – 1.20
ZZ (Two severely deficient genes)	0.20 – 0.45
Null/Null (two dysfunctional genes)	0

Alleles

Alleles are the pairs of genes on a chromosome. Humans have two AAT alleles, one allele inherited from each parent. The prefix "Pi", which sometimes appears before the allele, stands for protease inhibitor. Alleles were identified long before the *SERPINA1* gene was known and alleles were named with the Pi* prefix.

The normal AAT allele is the Pi*MM (i.e. MM) genotype. People with M alleles have normal AAT levels. [4] There are also M subtypes e.g. M_1, M_2, and M_3. The AAT concentrations are similar in people with M_1M_2 and M_1M_1 phenotypes and increased in M_2M_2.

AAT Blood Levels

Different concentration levels of AAT in the blood vary by author. The following concentrations are relative to normal levels and are a guide only:

- The SS and MZ genotypes express around 60%
- The ZZ genotype expresses around 10-15%
- The SZ genotypes expresses around 25-40% [7]
- The MS genotype expresses around 80% [8; 9]
- The Null/Null genotype is thought to have a total absence of serum AAT [7]

Disease Risk and Genotype

The level of AAT and how it behaves is associated with deficiency and risk of disease:

- no risk (MM)
- moderately risk (MZ, SS, MNull, FS, M1M$_{Heerlen}$, MF, MI and SI)
- high risk (ZZ, SZ, Null, FZ, NullNull, ZI and SNull [3; 10]
- Paediatric / childhood liver disease can occur but is rare. Some children may face a liver transplant at an early age.
- SS genotype has been associated with an increased risk of lung-cancer, however, different studies have reached different conclusions about risk. [10; 8]
- Null/Null, is thought to have the worst lung function and more severe emphysema. [7]
- Most MZs have a low risk of A1AD illnesses, however, some develop gallstones and others may develop liver and / or lung problems (exacerbated by smoking). [11]

Rare (Including Very Rare Variants)

Examples of rare phenotypes include: ZZ, Null, FM, FS, FZ, PM, XM, YM, IM, TS and EP but not all cause serious disease.

- Z, Null, P, F, I, P, T, are associated with deficiency.
- The F variant makes normal AAT levels but is considered dysfunctional in its ability to inhibit neutrophil elastase (which may cause elastase-induced lung damage) but when paired Z F, this genotype may be susceptible to emphysema (12)
- The TS variant appears to have lower levels of AAT than TM
- The P phenotype variant when associated with M doesn't appear to cause harm
- The I phenotype has no clear disease association
- The E, X and Y are not known to be associated with deficiency (13)
- The clinical features of the Iners phenotype are not known.

Other rare variants are named after locations e.g. SRoubaix, WSanit-Avre, M1Lille, M1Lyon, and Granite Falls, some of which are classified as benign while others are assumed to be Null. (14)

- The King's phenotype is associated with neonatal jaundice and emphysema.
- The Mmineral springs and the Mprocida phenotype have a high risk of emphysema in homozygotes.
- MMalton, Siiyama and Z phenotypes are considered severe deficiency alleles associated with liver disease and emphysema in homozygotes. (15)
- The MMalton variant is also known as Mnichinan and Mcagliari and can mimic the Z phenotype (with both liver and emphysema risk). (16)

The way dysfunctional genotypes behave can vary for example:

- Pittsburgh has an amino acid substitution and an off-target recognition of some proteases (but not neutrophil elastase) (1)
- The variant known as Iners, is inactive. (1)

Carrier

The term 'carrier' is sometimes used when an individual has one deficient (mutated) AAT gene, however, the term carrier is now considered misleading by many as people with one abnormal gene can develop illness e.g. MZs can develop gallstones, lung or liver disease.

Clinical Trials (See Gene Editing / Gene Therapy)

A number of clinical trials have commenced looking at different ways to cure A1AD using genetic technologies. For example, trials are attempting to stop the accumulation of antitrypsin in the liver, or stop AAT production while delivering normal AAT to the lungs.

Diagnosis

Guidelines suggest testing close relatives of someone diagnosed. Lab tests will measure the level of AAT in the blood. As current testing usually only identifies Z or S variants, genetic testing may be required.

Genes

Genes are made of DNA that encodes a trait. Genes carry instructions that determine what the body is like, how it functions and survives.

Gene Editing / Gene Therapy (see Clinical Trials)

Gene therapy has advantages over augmentation therapy (AAT infusion) as it promises to be a one-off injection. Gene therapy aims to deliver normal human M type AAT complement DNA, using a gene transfer vector so normal protein is secreted after a single injection. [3]

Genetic Counselling

Genetic counselling aims to help people understand and adapt to a diagnosis.

Genotype

A genotype is the set of genes that the person carries, inherited from both parents.

Genotyping

Genotyping is the process of identifying differences in genetic make-up of an individual.

Heterozygous

Heterozygous means that someone has inherited different forms of a particular gene from each parent e.g. MZ (M from one parent and Z from the other).

Homozygous

Homozygous means that you have two identical forms of a particular gene (one from each biological parent e.g. ZZ).

Medicare Benefits Schedule (MBS)

The Medicare Benefits Schedule number for testing for AAT is item 66635. [17] If not bulk billed, the fee is $20 for item number 66635 and $49.50 for item number 66638. [8]

Phenotype

A phenotype is the observable characteristics in a person. Phenotypes are influenced by genes and sometimes the environment. Severity of disease is often linked to phenotype.

Prevalence

Approximately one in nine people have at least one faulty gene.

Risk factors

To minimise lung damage alphas should avoid dust, smoke, gas, chemicals and pollutants. [5] Lung exacerbations (e.g. a bacterial lung infection) are linked to accelerated progression of lung damage. Antibiotics should be taken at the first sign of a lung infection. Some doctors provide "rescue'' antibiotics to assist with rapid treatment. Treatment with augmentation therapy is associated with a reduced risk of emphysema. To minimise liver damage alphas should avoid alcohol consumption.

Table 2: Risk of Emphysema and Liver Disease by Phenotype

Genotype	Risk of Emphysema	Risk of Liver Disease
ZZ	High	Increased
SZ	Low to Medium	Increased
MZ	Low	Low
Null-Null	High	No increase
SS	Low	No increase
MM	No increase	No increase

Liver Related Words and Issues

Ascites
Ascites is the build-up of fluid in the abdomen which can occur when the liver isn't working properly e.g. due to cirrhosis.

Bilirubin
Bilirubin is a waste material produced by your liver and your bile excretes bilirubin from your body.

Cirrhosis
Cirrhosis is scarring in the liver. Liver disease is highly variable in A1AD but the risk increases with age. (18)

Cholestasis
Cholestasis is a type of liver disease. It happens when bile from the liver is reduced or blocked which can lead to a build-up of bilirubin. The two types of cholestasis are intrahepatic and extrahepatic and both can cause jaundice (a built up of bilirubin, a waste material in the blood)

Fatty Liver
Some patients with A1AD have a "fatty liver". Fatty liver is linked to being overweight, type 2 diabetes, eating refined carbohydrates, eating sugar and impaired gut health. Losing weight and avoiding overeating can help remove liver fat and reduce the risk of developing a more serious condition called non-alcoholic liver disease.

Fibrosis
It is thought that approximately 25% of severely deficient Alphas may have fibrosis. (19)

Gamma Glutamyl Transferase (Gamma GT or GGT)
Gamma GT can indicate obstructive or cholestatic liver disease. This liver enzyme indicates that bile is not being carried properly away from the liver due to bile duct blockage. The GGT test together with the ALP liver test may indicate that bile flow is altered if both are increased.

Hepatocellular Carcinoma
A type of liver cancer.

Liver Function Tests / Liver Panel / Liver Profile
Your doctor may order liver function tests (LFT) to detect and monitor acute or chronic liver inflammation or disease. The tests look at clotting factors, proteins and elevated enzymes. A painless test called a Fibroscan, is usually recommended.

Neonatal Hepatic Syndrome
Neonatal hepatic syndrome occurs in a small number of A1AD newborns. This syndrome is believed to be an acute response to polymerization of the Z-type protein within hepatocytes and a liver transplant may be required.

Polymers
The retention and polymerisation of αlpha-1 antitrypsin within the tissue of the liver is sometimes called polymer. The trapped polymers are associated with neonatal hepatitis, cirrhosis and hepatocellular carcinoma.

Portal hypertension

The portal vein is a blood vessel that carries blood from the gastrointestinal tract, gallbladder, pancreas and the spleen to the liver. A thrombosis (a blood clot within a blood vessel) in the portal vein or varices (enlarged / swollen veins) in the spleen can lead to portal hypertension and reduction in blood flow.

Protease
Protease is an enzyme designed to break down proteins.

Lung Related Words and Issues

The Active Cycle of Breathing Technique (ACBT)
See the Alpha-1 Organisation Association's (A1OA) Fact Sheet *Lung Health.*

Airway Clearance Techniques (ACT)
See the A1OA Fact Sheet *Lung Health.*

Alveoli
Alveoli are fragile air sacs located at the end of the bronchial tubes.

Anticholinergics
Anticholinergics act as bronchodilators and are sometimes prescribed to treat COPD.

Arterial Blood Gas
An arterial blood gas (ABG) test indicates the levels of oxygen (O_2) and carbon dioxide (CO_2) in an artery. The test indicates how well the lungs are functioning i.e. how well oxygen can enter and carbon dioxide can be removed (i.e. gas exchange).

Asthma
Adult asthma is sometimes given as a misdiagnosis to lung affected people with A1AD. A1AD can coincide with asthma but people with A1AD don't always have asthma. Patients with both asthma and A1AD are more susceptible to accelerated and progressive loss of lung function. Almost 50% of A1AD patients have been misdiagnosed with asthma or allergic disease. [(4)]

Augmentation Therapy
In some countries a weekly infusion of purified plasma, containing AAT protein, is given to raise the circulation of AAT to a protective level with the aim of maintaining lung function and slowing lung decline. [(3)] Augmentation therapy is the only non-surgical treatment available for lung affected people. Augmentation therapy is not funded by the Australian Government, however, the product is registered with the Therapeutic Goods Administration (TGA) so it can be privately purchased if prescribed by your doctor via a program called the Special Access Scheme (SAS).

Bronchial Valves (see Zephyr Valves)
Bronchial valve placement may be considered in selected patients with A1AD.

Bronchodilator
Bronchodilators are a type of medication designed to make breathing easier. They relax the muscles in the lungs and widen the airways (bronchi). Bronchodilators may be prescribed to treat chronic lung conditions such as asthma and emphysema.

Bronchiectasis
Bronchiectasis is a structural change (widening or scarring) of the bronchial tubes in the lungs

(i.e. in the airways) and is associated with the unopposed neutrophils. [4] Bronchiectasis can affect one or many sections of one or both lungs and puts individuals with A1AD at risk of repeated lung infections as the dilated bronchial tubes trap mucus.

Bronchiolitis

Bronchiolitis is a common lung infection in children causing inflammation in the small airways. It is different from bronchitis. The main difference is that bronchiolitis involves the small airways that branch off the bronchi (the bronchioles) and bronchitis is inflammation of the airways that lead to the windpipe.

Bronchitis

Bronchitis is chronic inflammation of the bronchial tubes (the airways leading to the windpipe) associated with excess mucus production.

COPD

COPD stands for Chronic Obstructive Pulmonary Disease. The management of COPD in A1AD is usually similar to non-genetic COPD management. COPD is an umbrella term associated with progressive lung diseases including emphysema, bronchitis and bronchiectasis. A1AD contributes to 3-4% of people diagnosed with COPD but some people receiving a COPD diagnosis may not realise that they also have A1AD. [20]

Corticosteroids

Both inhaled and oral corticosteroids may be prescribed for individuals with A1AD. Oral corticosteroids are more likely to be prescribed if diagnosed with a lung infection. Corticosteroids lower inflammation and reduce immune system activity.

CPAP / Continuous Positive Airway Pressure

CPAP or continuous positive airway pressure is a therapy that ensures that a lung affected person can breathe normally during sleep. A mask is worn while sleeping, attached to an adjustable air pump, so that air pressure can be delivered at a constant or variable rate so normal breathing can occur. Portable CPAP machines are also available. Oxygen therapy can be incorporated into CPAP therapy.

Elastin

Elastin is a protein found throughout the body, however, elastin fibres make up a large percentage of total protein in the lung (e.g. of connective tissue). Elastin gives elasticity and stability to the lung and can be damaged following a lung infection, resulting in lung damage.

Emphysema

In A1AD, emphysema can result when damage occurs to the walls of the air sacs (alveoli) of the lung, moving less oxygen into the blood.

Exacerbations

A lung exacerbation or a flare-up is a worsening of lung symptoms beyond usual day to day variability (e.g. a bacterial lung infection). In A1AD patients, early treatment of exacerbations with antibiotics is associated with improved health outcomes.

Gas exchange

The main purpose of your lungs is gas exchange i.e. getting oxygen into the blood and removing carbon dioxide.

Hypoxia
Hypoxia is a deficiency in the amount of oxygen reaching the tissues e.g. when there is low arterial oxygen supply and the supply of oxygen is insufficient for normal life functions. Hypoxia activates neutrophils in A1AD.

Lung Transplant
See the A1OA brochure on Lung Transplant.

Lung Volume Reduction
Lung volume reduction, a surgical procedure to remove diseased lung tissue, is not usually recommended in A1AD. Caution is raised by some researchers due to a higher 2-year post-surgery risk of mortality. [21]

Non-tuberculosis Mycobacterial Disease (NTM)
Non-tuberculosis mycobacterial is a general term for a group of bacterial disorders caused by common bacteria found in the environment (in water and soil). NTM disease is more common in people with lung damage e.g. bronchiectasis.

Neutrophil Elastase (NE)
Neutrophil elastase is a protease enzyme. AAT is an anti-protease and is the most active inhibitor of neutrophil elastase. [22] Neutrophils are produced in bone marrow, carry and release proteases. NE circulates in blood into the pulmonary capillaries putting the alveolar in the lung at risk of progressive non-reversible damage leading to emphysema. [3]

Oxygen / Liquid Oxygen / Oxygen Therapy
Supplemental oxygen may be required to ensure adequate oxygen levels. Oxygen may be prescribed when flying, sleeping, exercising or for day and night use. Individuals with severe airflow obstruction have better survival if they use their oxygen supplementation regularly (e.g. day and night).

Pulmonologist
A pulmonologist is a doctor specialising in lung health. In some countries they are called respirologists.

Pneumonia
Pneumonia is an infection in one or both lungs and can be caused by viruses, bacteria or fungi. The pneumonia vaccine is recommended to Alphas who are lung affected.

Pulmonary Rehab (Rehabilitation)
Pulmonary rehabilitation is a comprehensive intervention including exercise training, education and behavioural change and is typically prescribed for patients with emphysema.

Pulse Oximeter
An oximeter is a small device usually clipped onto the finger that reads blood oxygen levels. Normal oximeter readings range from 95 – 100%. Values under 90 are considered low and supplementary oxygen may be prescribed.

Spirometry
Lung function tests called spirometry assess how well your lungs work. You sit and breathe into a machine called a spirometer which records the amount of air you breathe in and out and the speed of your breath. Results include FVC, FEV_1, FEV_1/FVC ratio and gas exchange.

- The FVC test measures how much you can forcefully breath out after breathing in as deeply as possible. A lower than normal reading may indicate something is restricting or obstructing your breathing.
- The FEV_1 stands for forced expiratory volume and indicates how much air you force out in one second. A significant low reading may indicate a breathing obstruction.
- The FEV_1/FRC ratio is calculated to represent your lung capacity related to how much that you can exhale in one second. A low reading is linked to something blocking your airways.
- Lung diffusion testing (gas exchange) looks at how well your lungs allow oxygen and carbon dioxide to pass in and out of your blood.

Sputum

Sputum is mucus coughed up from your respiratory tract, usually from an infection, pneumonia, bronchiectasis or bronchitis**.** The body makes sputum to remove foreign matter from the lungs.

Vaccines

You should speak with your health provider about recommended vaccines for example, an annual influenza vaccination, Pheumovax® vaccines, Hepatitis A and Hepatitis B vaccine.

Zephyr Valve

A Zephyr valve is a small valve that is placed in the airways to improve breathing, exercise capacity and quality of life in people with severe emphysema. The valves block damaged regions in the lungs, allowing the healthy part of the lung to work more efficiently. The valves close when you breath in, preventing air from entering the damaged areas of the lungs. Zephyr values are one brand of endobronchial valves.[(23)] Patient eligibility is dependent on a number of issues including lung hyperinflation, extent of lung damage, residual volume and FEV_1.

Other Effects of Lower than Normal Alpha-1 Antitrypsin Levels

Autoimmune Disorders (see Vasculitis)

Vasculitis is associated with A1AD. Other autoimmune diseases have been associated with A1AD including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and have been found to be higher in A1AD.

Granulomatosis with Polyangiitis (see Vasculitis)

'Poly' means that many blood vessels are involved and 'angiitis' indicates that arteries are involved. This uncommon condition causes inflammation of the blood vessels in the ears, sinuses, nose, throat, lungs and kidneys. This condition was previously called Wegener's granulomatosis. Prompt diagnosis is required. Treatment includes drugs to suppress the immune system.

Inflammation

Inflammation can occur in the lungs, blood vessels (vasculitis), subcutaneous fat (panniculitis); and, the liver (hepatic inflammation).

Panniculitis

See the A1OA Fact Sheet on Panniculitis.

Vasculitis

Vasculitis is inflammation of blood vessels.

Common Tests

CT Scan
A CT chest scan is often used to diagnose emphysema. A baseline CT scan is recommended for people with abnormal lung function.

Laboratory / Blood Tests
Genotyping can also be ordered by your GP or specialist but is not currently covered by the MBS and may cost between $65 to $100. Not all laboratories undertake genotyping.

Lung Tests
Pulmonary function testing, spirometry, lung function tests, post-bronchodilator, bronchoscope, arterial oxygen, gas exchange, and sputum cultures are all associated with seeing how your lungs are working and if lung disease is present. (See CT scan).

Liver Tests
See liver function tests.

Ultrasound
An ultrasound may be used to take images of your liver and other organs.

Where to go for information and support
Alpha-1 Organisation Australia (A1OA): email: contactus.a1oa@gmail.com

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This brochure sheet is one in a series of information sheets produced by the Alpha-1 Organisation Australia (A1OA), a not-for-profit charity registered with the Australian Charities and Not-for-profits Commission (ACNC). This information is designed to be a guide only and does not replace advice given by your health professional. Any treatment information or brand names are correct at the time of printing. If the information raises concerns or if you have further questions please consult your doctor.

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