



Diagnosis and Treatment



A guide for medical professionals working with people diagnosed as having the genetic condition
Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (AATD) is one of the most common serious hereditary disorders. AATD has been identified in virtually all populations but is most common in individuals of Northern European (Scandinavian and British) and Iberian (Spanish and Portuguese) descent. Among patients with Chronic Obstructive Pulmonary Disease (COPD), 1 to 3% are predicted to have AAT Deficiency. It can also cause life threatening liver damage in adults and children and liver cancer in adults. Panniculitis and vasculitis caused by AATD is observed occasionally. Despite its prevalence, patients and healthcare providers have been poorly informed about the disorder. For this and other reasons, the overwhelming majority of individuals with AAT Deficiency have not been detected.

This guide is for medical professionals caring for patients with AATD. We also produce other booklets for those affected & their families.

What is Alpha-1 Antitrypsin Deficiency?

Alpha-1 Antitrypsin (AAT) Deficiency is a genetic disorder characterised by the production in the liver of an abnormal AAT protein. The liver cells cannot secrete this abnormal AAT protein which accumulates within the cells and results in a marked reduction of circulating AAT levels. Although the mechanisms are not completely known, it is believed that the retained abnormal AAT protein over time leads to liver injury in some affected persons. In the lungs low-levels of AAT allow for the destructive effects of neutrophil elastase to go unchecked. This results in damage to the delicate gas exchange region of the lungs (alveoli), eventually leading to emphysema in people as young as 30 years of age. Thus, people with AAT Deficiency are at high risk of developing life-threatening liver and lung disease.

Molecular Biology

The gene encoding AAT is located on the long arm of chromosome 14 within the q31-32.3 region and it named SERPINA1 or Protease inhibitor (Pi). There are many hereditary variants of the Pi gene. The most frequent occurring family of alleles is described as PiM. The most common alleles leading to AATD are PiZ and PiS. A series of null alleles (designated PiQ0 or Pi_{null}) is associated with the most severe deficiency, producing no active AAT or less than 1% of the normal amount in the plasma.

There are more than 100 different allelic variants of AAT but most of these are very rare.

Genetics

The two most important genetic aspects of Alpha-1 antitrypsin deficiency are the understanding that there are many alleles for the protein and that the clinical manifestations (lung and liver disease) result from specific combinations of alleles.

Because both alleles (paternal and maternal) can be detected the hereditary mode is called co-dominant. In a given individual the phenotypes (protein types) describe both alleles: PiMM, PiMZ, PiZZ, PiSZ, etc.

| <i>Phenotype</i> | <i>What Does It Mean?</i> |
|----------------------|--|
| Pi ZZ (Homozygote) | Patient has Alpha-1 antitrypsin deficiency |
| Pi MZ (Heterozygote) | Patient is a CARRIER of Alpha-1 antitrypsin deficiency and can pass these genes on to their children |
| Pi MM | Patient does NOT have Alpha-1 antitrypsin deficiency |

Clinical Manifestations

Clinical manifestations are always present in patients with complete absence of serum alpha-1 antitrypsin (null variants). The majority of patients with ZZ or SZ genotypes, and some with the SS genotype, have pulmonary or hepatic symptoms. Heterozygous individuals, with both a normal and a variant allele (MZ or MS) sometimes develop clinical symptoms.

Emphysema

Pulmonary emphysema is described as an irreversible distension of the lungs as a result of the destruction of pulmonary tissue. AATD patients tend to present with the following profile:

- Pulmonary emphysema in young adults (before the age of 45)
- Pulmonary emphysema without typical risk factors, such as tobacco smoking or occupational exposure to dust or airborne particles
- Pulmonary emphysema predominantly of the lower lobes
- Chronic hepatitis without other explanation
- Family members with pulmonary disease or ancestors with pulmonary emphysema in young adulthood, bronchiectasis, or liver cirrhosis

In the case of interstitial pulmonary diseases such as sarcoidosis and idiopathic fibrosis, pulmonary emphysema may occur in serious forms at a later stage of the disease. Even without the assistance of a pulmonary function test, pulmonary emphysema can be clinically determined and distinguished from chronic bronchitis.

Emphysema

- Medical history of smoking
- Little evidence of coughing
- Barrel-shaped thorax
- Reduced respiratory breadth
- Weakened respiratory sounds
- Hyper-sonorous percussion sound
- Dyspnoea on exertion

Bronchitis

- Medical history of smoking
- Constant coughing and expectoration
- *not applicable*
- *not applicable*
- Dry rhonchi
- *not applicable*
- Dyspnoea with exacerbation

Around 1 to 3% of all emphysema patients have a congenitally serious Alpha-1 antitrypsin deficiency (AATD). In view of the fact that not all people suffering from emphysema have been diagnosed as such, the number of people with AATD cannot be specified with any precision.

If figures from the neonate screening in Sweden are taken as basis, 1 out of every 1,700–5,000 Caucasians is affected by AATD. Assuming 728 million Europeans, this is 145,000-425,000.

Identification of Patients

The recommendation of the World Health Organization (WHO) is that all adult patients with the following problems should be tested for AATD:

- COPD
- Asthma
- Family history of AAT Deficiency
- Chronic liver disease

Other conditions not specifically recommended by WHO, but possibly indicating increased risk for AAT Deficiency include:

- Bronchiectasis
- Panniculitis
- Unexplained vasculitis, particularly of Wegener's granulomatosis type
- Hepatocellular carcinoma
- Any evidence of unexplained liver disease

If these conditions are seen in non-smokers of any age, or if COPD occurs at an early age (30 to 55) in smokers, the likelihood that AAT Deficiency is a causative factor is increased.

Lung Function Tests

Pulmonary function testing is an important means of diagnosing COPD and for monitoring its progression. Spirometry is frequently used for recording long-term deterioration of patients through changes in forced expiratory volume in 1 second (FEV1). The annual loss in healthy people is approximately 30ml, this rises to 100ml in severely AAT deficient patients. FEV1 measurements require a lot of cooperation from the patient and a number of attempts may be needed to gather reliable data.

As emphysema progresses the vital capacity (VC) may slowly increase. Whole body plethysmography is required for more precise determination of this. Other tests that may be found to be necessary are for increased airway resistance (Raw) and elevated residual volume (RV).

Measurement of carbon monoxide diffusion capacity (DLCO) is another technique of lung function testing. This shows the global gas exchange potential between the alveolar space and the pulmonary capillaries. AATD patients have a DLCO of $50 \pm 22\%$ of normal values.

Biochemical Tests

If AATD is being considered in a differential diagnosis a quantitative serum analysis should be conducted. This measurement is inexpensive. It is recommended that C-reactive protein (CRP) is assessed at the same time because AAT that may be elevated during inflammation and so appear deceptively normal in patients with medium grade deficiency. Simultaneous measurement of CRP will help identify this possibility.

The normal serum concentration in adults is 1.5 to 2.5 g/L. Sometimes the concentration is expressed in micromoles per litre – these figures are roughly 20 times the value when expressed in grams per litre. Homozygotic PiZZ patients typically have a serum level of AAT less than 0.3 g/L. The minimum protective level is generally accepted to be 0.8 g/L

Phenotyping is a more complex analysis which measures the electrophoretic mobility of the AAT molecules. The conventional names of the alleles are based on this test: F (fast: anodic), M (medium: moderate mobility), S (slow anodic mobility), Z(cathodic).

The more common M, S and Z alleles may be detected by genotyping using a polymerase chain reaction (PCR) to amplify the point mutations which are then detected by various means. This process is becoming more popular and can be cheaper than IEF. If a rarer allele is suspected and a suitable PCR probe is not available then genetic sequencing may be performed. This is a more expensive option and only needed when the clinical picture is confused.

Radiology

Chest radiographs which show emphysematous changes on the basal regions of the lungs the central and peripheral sections are also affected. Bullous changes are not unusual in alpha-1 antitrypsin deficiency. Thickening of the bronchial walls and peripheral dilation are rare pulmonary changes.

Computed tomography (CT) allows more detailed visibility than conventional chest radiography. The base of the lungs tends to be more affected by the destruction of the lobular alveoli than in other forms of emphysema. Additionally, pronounced vascular loss can be detected in the peripheral lungs. In chronic bronchitis associated with AATD bronchial wall thickening is more pronounced than in chronic bronchitis caused by smoking.

Ongoing Care

After confirming AAT Deficiency the following baseline data should be collected for monitoring the progression of the condition:

- Posteroanterior (PA) and Lateral Chest X-Ray or a high resolution CT
- Pulmonary function tests, including:
 - Spirometry curves (before and after inhaled bronchodilator)
 - Lung volumes, Diffusion capacity (DLCO), Arterial blood gases
- Liver biochemical tests (AST, ALT, Bilirubin, Albumin, etc)
- Liver ultrasound examination

Treatment

The forms of treatment listed in this guide for the confirmed AATD patient are:

Behavioural & Lifestyle Change

Drug Therapy for Lung Problems

Specialised Therapy for AAT Deficiency

Surgical Options.

Behavioural & Lifestyle Change

Alpha1 Awareness publishes Living with Alpha-1 a lifestyle guide for people diagnosed as having the genetic condition Alpha-1 Antitrypsin Deficiency.

Individuals with AATD should NEVER smoke. Evidence shows that smoking tobacco products significantly increases the risk and severity of emphysema in AATD individuals and may decrease their life span by ten years or more. Exercise and nutritional plans also contribute to maintaining a healthy body, which places less stress on the lungs. These three issues are explored in further detail below:

Smoking Cessation This is the first priority in managing patients with AATD. Lifelong non-smokers will have a better chance of avoiding serious lung disease. Current smokers should stop smoking upon diagnosis, this is because the most severe lung function impairment is seen in current or former smokers. Smoking attracts white blood cells to the lungs in large numbers and speeds the development of lung disease. The lungs in AATD patients do not have the normal defences against the white blood cells and neutrophil elastase.

Avoiding Environmental Pollution Although formal studies are lacking, it is advisable for Alphas (persons with AAT Deficiency) to avoid occupational and environmental pollutants that can be inhaled (including pollen, dust, areas with high levels of air pollution, and second-hand tobacco smoke). These substances can cause further irritation of the lungs and worsen the current condition of the patients with disease. Avoid both indoor and outdoor air pollution such as particulates smaller than 10 μm (found in higher industrialised urban regions) and exposure to aerosol sprays. Alphas may encounter pollutants and infections both at home and at work, thus there are two sets of recommendations.

In the Workplace

Patients should avoid exposure to inorganic or organic dust (brick, hay, etc.) or irritating gasses (i.e. chlorine, isocyanates, etc.). Patients should seek the healthiest possible work environment, and have clean indoor air, with proper ventilation and filtration systems and avoid second-hand tobacco smoke whenever possible. They should wear protective clothing (gloves, etc.) when handling any type of chemical compounds since these may be absorbed through the skin and could further damage an already compromised liver. Read labels carefully and be aware of potential dangers from these agents.

In the Home

Patients should be advised to avoid the following in the home: chlorine and ammonia (found in some household cleaning products), pesticides, fireplace smoke, aerosols, powders, etc.

Since bacterial and viral infections are harmful to the lungs, patients should also be advised to try to avoid contact with sick or infectious people. Handwashing with an antibacterial soap is the best way to avoid both contracting and spreading infectious diseases.

Development of an Exercise Programme

Routine exercise can improve mental outlook, stamina and physical well being. Exercise is essential to all Alphas.

Supervised aerobic and strength exercises should begin as soon as possible after diagnosis.

Walking, strolling, swimming, and/or cycling can facilitate exercise, which may be beneficial in improving lung function and endurance.

It is important for all Alphas to have personally tailored exercise programmes carefully monitored an exercise specialist. Patients should start exercising slowly and increase levels of exercise over time as their tolerance for exercise increases.

A Pulmonary Rehabilitation programme is highly recommended for Alphas. This can help an individual with pulmonary disease through exercise, breathing retraining, education, smoking cessation, and nutrition counselling. The programme must be tailored to the patient's specific needs.

Alcohol Consumption Alcoholic beverages can damage the liver even in normal people. Many authorities recommend low, infrequent or no alcohol consumption for PiZZ patients. Patients with any indications of AAT-related liver damage should avoid alcohol completely.

Development of a Nutrition Programme Although there is a lack of formal research regarding the effects of specific dietary recommendations, proper eating habits may help to preserve lung and liver function. It is important for your patient to maintain an ideal body weight, whether he/she has lung/liver disease or not. Since scientific research indicates that people with lung disorders need to consume more calories than healthy people, this affects the manner in which your patient should approach nutrition. Supportive nutritional needs in those patients exhibiting liver complications due to AATD are highly case-specific. Since sodium and protein intake may become a concern in patients with liver failure, good dietary advice is recommended. In the AATD patient who exhibits signs of liver complications, fat absorption may be altered; therefore some physicians recommend supplementing the diet with vitamins A, D, E, and K. The dietary requirements of an infant experiencing feeding difficulties are best referred to a specialist in this field. Recommend to your patient that he/she should establish or maintain good eating habits. If your patient has lung and/or liver problems it may help to work closely with a dietician, who will be able to set up an appropriate, individualised nutritional plan.

Reducing Stress Persons with AAT Deficiency (Alphas) report benefits with stress reduction techniques. There are many relaxation techniques that help in reducing stress. Here are a few:

| | | |
|---------------------|--------------------------|-------------|
| Breathing exercises | Muscle relaxation | Biofeedback |
| Hypnotherapy | Positive thinking | Yoga |
| Meditation | Improving sleep patterns | |

Drug Therapy for Lung Problems

This is among the most important type of medical therapy for the newly diagnosed individual with AAT Deficiency.

Vaccinations It is important for Alpha patients to have a yearly influenza vaccine and a pneumococcal bacteria vaccine every five to six years. Since his/her lungs are vulnerable to pollutants and infections, the use of these prophylactic vaccinations is of the utmost importance.

Effective vaccines are available for hepatitis A and B. These are especially important in patients with established liver disease.

Recommendations:

Annual influenza vaccine
Hepatitis A vaccine
Hepatitis B vaccine
Pneumococcal polysaccharide vaccine (PPSV)
- administration or confirmation every 5 to 6 years

Aggressive Treatment of Lung Infections Prompt and aggressive treatment of infections is recommended due to the increased neutrophil elastase burden during infection. It is important that Alphas seek immediate professional medical advice at the first indications of a lung infection. Here is a list of common symptoms they should be aware of::

Fever
Chills with fever
Increased coughing - may not be productive
Increased shortness of breath
Changes in colour of phlegm

Because the lungs attract more leukocytes when an infection is present, and the leukocytes release neutrophil elastase, it is important to control lung inflammation. Steroids may be prescribed to reduce the severity of exacerbations. Antibiotics may be given to reduce the effects of the causative or opportunistic bacteria. Suitable patients may be given a supply of steroids and/or antibiotics to be kept at home in line with NICE Guidance on COPD.

Another piece of preventive advice for the patient is:

Avoid people who are sick - infected individuals
Avoid children under five years of age
- often infectious or exposed to infections

Aggressive Evaluation of Liver Complications It is important for parents, caregivers or social care workers to be aware and advised of any indication of complications related to liver disease. Here is a list of common symptoms that may require therapy:

- Increased abdominal swelling - ascites
- Coughing up or vomiting bright red blood
- Blood in stools or blackish/purplish stools
- Little or no urine
- Dark urine
- Fever Lack of energy, easily fatigued
- Confusion, unusual crying, disorientation, lethargy
- No appetite/refusal to eat or drink
- Itching or increased itching
- Peripheral edema
- Change in, or the appearance of, jaundice

It is very important to inform the individual to read carefully the labels on over-the-counter medications and to be certain to inform the healthcare provider if alternative medicine or vitamin supplements are being taken.

Bronchodilators Bronchodilators may be useful in relieving the symptoms of AAT Deficiency. Depending on the specific medical history and present condition of the patient, bronchodilators may be advisable. Short acting β_2 sympathomimetics (Salbutamol, Terbutalin, etc) are the medication of choice to treat obstruction caused by the smooth muscles of the small bronchi. A combination of β_2 sympathomimetics and anticholinergics is currently recommended as first-line treatment for symptomatic patients with obstructive disease of the airways. In long-term treatment, the long-acting anticholinergic tiotropium is assumed to be superior to the short-acting ipratropium.

Corticosteroids Inhaled corticosteroids can be useful as a preventative treatment for AATD and oral corticosteroids may be helpful during exacerbations. Prednisolone is found to lead to faster improvement in FEV1 than placebo. However, the positive effect wears off after 14 days. Typically the dose is reduced over fourteen days to minimise signs of adrenal insufficiency.

Supplemental Oxygen For people who need supplemental oxygen, it has been shown to be lifesaving. Oxygen can be important for individuals with low blood oxygen levels, during active infections and/or with progressive destruction of the lung tissue. Supplemental oxygen may be needed during exercise and/or sleep. Supplemental oxygen is also recommended during exercise. For some Alphas, it is especially important when travelling by air, because cabin pressure is reduced at altitude.

Surgical Options

Lung Volume Reduction (LVR)

Lung Volume Reduction is especially promising in the case of target zones in the apical lungs. There is some concern about the outcome in the case of basal pulmonary emphysema which is typical for AATD patients. Studies have shown that AATD patients return to baseline figures after 6 to 12 months. Further deterioration is found after 2 years.

However, with carefully selected patients LVR and other thoracic surgical interventions such as bullectomy may be found to be beneficial.

Organ Transplantation of Lung or Liver

Lung/liver transplantation is becoming a viable option for some patients. As experience with new surgical techniques (particularly single lung transplantation) increase, lung transplantation may become more attractive to AATD patients with end-stage lung disease.

Living donor transplant is also a possibility where a suitable healthy adult is prepared to donate a part of his or her liver. This is an increasingly popular option for liver transplantation in children.

Large volume paracentesis (LVP) may become necessary in end-stage liver disease when diuretic therapy is inadequate in the treatment of ascites. Portal vein decompression utilising surgical shunts is an effective means of relieving intractable cirrhotic ascites and in the treatment of portal hypertension when there is evidence of esophageal varices. The portal caval shunt surgical procedure may be used if more conservative measures utilised in controlling bleeding, such as sclerotherapy or band ligation, are ineffective. The TIPS (transjugular intrahepatic portosystemic shunt) procedure has also been effective in controlling bleeding from esophageal or gastric varices in addition to controlling cirrhotic ascites.

Surgical treatment options are highly individualised to each patient. As with all surgery, outcomes depend on a number of issues specific to each person. There are no guarantees for the extent to which there will be improvement of medical condition.

Specialised Therapy for AAT Deficiency

Replacement therapy involves giving an intravenous infusion of human alpha-1 antitrypsin. This has been performed in the United States, Canada and some European countries since 1987.

Current NHS/NICE guidelines do not recommend replacement therapy for patients with any severity of AATD emphysema.

Replacement therapy has been found to be a very effective treatment for panniculitis and treatments have been available in the United Kingdom on a Named Patient Basis.

Liver & Lung Support Groups

We support everybody as much as we can. Our board members are not medically trained, so are unable to offer medical advice. For medical questions, you always should speak to your GP or specialist.

Children

Liver



Children's Liver Disease Foundation

www.childliverdisease.org

Children's Liver Disease Foundation (CLDF) was formed in 1980 and is a unique national charity dedicated to taking action against the effects of all liver diseases of childhood. Based in Birmingham, CLDF is a comprehensive information hub for healthcare professionals and the general public, a tailored support service for children, young people and young adults with liver disease and their families.

Adults

Liver



British Liver Trust

www.britishlivertrust.org.uk

They support patients and families, so you don't have to face liver disease alone. They campaign to improve awareness so more people are aware of the risks to the liver.

Lung



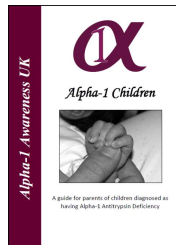
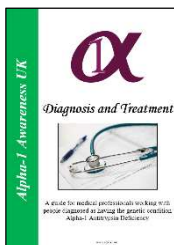
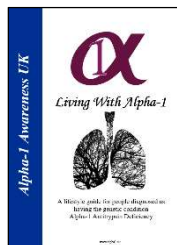
British Lung Foundation

www.blf.org.uk

They are the only UK charity looking after the nation's lungs. They have full support for lung affected people by phone, their online web community and also through their local support groups.

Our other publications

We produce booklets for those who need more information on Alpha-1.

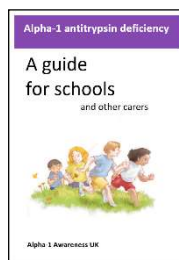
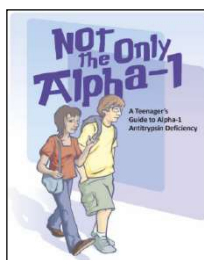
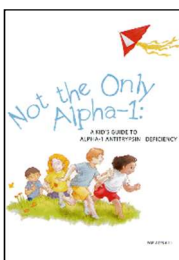
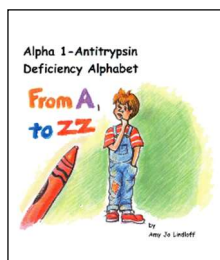


Living with Alpha-1 – Information people need when they have just been diagnosed. A lifestyle guide for Alphas.

Your Child's Liver – For parents of an Alpha child, how to help them.

Diagnosis and Treatment – A guide for medical professionals working with Alphas

We also have booklets for the younger ones:



From A to ZZ – Designed for younger children 4 - 8

Not the Only Alpha-1 – For children aged between 8 – 11.

Not the Only Alpha-1 – For older children of 11 and up.

A guide for schools – For schools, playgroups and other professionals who look after children.

For more information please visit:
www.alpha1.uk

or write to:
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