

## Alpha-1 Antitrypsin Deficiency: Lung Disease

Chronic obstructive pulmonary disease (COPD) affects millions of people each year. Chronic means long term, obstructive means it is hard to get air in and out of the lungs. The most familiar diseases in this group are emphysema and chronic bronchitis. In emphysema there is damage to the walls of the air sacs (alveoli) in the lungs. The earliest symptom of emphysema is shortness of breath during activity. Later the shortness of breath can occur at rest also.



### What is Alpha-1 antitrypsin deficiency?

Most cases of emphysema are caused by smoking or other environmental factors. There is growing evidence that genetics can also increase the risk of developing emphysema. Alpha-1 Antitrypsin Deficiency, or more simply Alpha-1, is a genetic condition that causes diminished levels of the protein, alpha-1 antitrypsin, produced in the liver. People with Alpha-1 may never develop any medical disease from this genetic condition. Others with Alpha-1 can develop Alpha-1 lung disease, Alpha-1 liver disease or other medical problems associated with this protein deficiency. If you have Alpha-1, there are things that you can do to reduce your risk of disease. Most prominent among the things that can reduce the risk of disease is avoidance of tobacco smoke.

### Why do some people with Alpha-1 develop lung disease?

Alpha-1 antitrypsin protein is important in the protection of the lungs. Alpha-1 antitrypsin protein acts to protect the lungs' air sacs, or alveoli, from damage when the immune system is doing work to protect the lungs. One type of the body's own white blood cells, the neutrophil, releases a chemical called neutrophil elastase when it encounters inflammation or infection. Although neutrophil elastase can be helpful in protecting the lungs from attack, it can also damage the lungs and cause emphysema if not held in

check. Alpha-1 antitrypsin protein blocks elastase and protects normal tissue in the lungs. So, if there is not enough alpha-1 antitrypsin produced in and released by the liver, there will not be enough to protect the lungs' alveoli and emphysema or COPD develops. This is Alpha-1 lung disease. About 1 in every 3,500 people has severe Alpha-1. The majority of people who have Alpha-1 are of Northern European decent, especially Scandinavians, but it has been found in all ethnic groups.

## What are the symptoms of Alpha-1 lung disease?

People who develop Alpha-1 lung disease can develop shortness of breath by the time they are 40 or 50 years old, frequently earlier in those who smoke cigarettes. Some with Alpha-1 lung disease will develop bronchitis and eventual disruption of the normal architecture of the bronchial tubes and air sacs, such as bronchiectasis and emphysema. This can lead to recurrent episodes of cough, sputum production and even pneumonia. But shortness of breath is the most common symptom with developing Alpha-1 lung disease.

## What tests diagnose Alpha-1?

Because Alpha-1 related disease is COPD, the diagnosis is made by the same methods. Your doctor may have you do a number of tests to evaluate your breathing. These may include:

- Detailed medical history including family history of lung disease
- Physical exam,
- **Blood tests.** In addition, two special blood tests determine the diagnosis of Alpha-1 Antitrypsin Deficiency. Alpha-1 antitrypsin blood level, Pi-type or phenotype (structure of the protein made by the Alpha-1 gene), and genotype (testing the Alpha-1 DNA). In people with Alpha-1 lung disease, the blood level of alpha-1 antitrypsin will often be very low, less than 20 percent of the normal level. The phenotype (Pi-type) of the alpha-1 antitrypsin protein in a person is determined by identifying how the protein moves on an electrified gel. A normal protein is referred to as an M protein. A person with normal alpha-1 antitrypsin proteins is referred to as Pi MM. The most common abnormal proteins are S, Z and F. Sometimes a gene will make no protein; this a "null" gene. When you have two Z genes, you are Pi ZZ, and a person that is most likely to get Alpha-1 lung and/or liver disease.
- **Chest radiograph or Chest CT scan.** A chest x-ray may reveal that the lungs are hyper inflated due to emphysema. A chest CT will show a pattern of emphysema specific to Alpha-1. When the normal small air sacs (alveoli) of the lungs break down and consolidate, they look like large holes in the lung, like the holes in Swiss

cheese. In those who smoke but don't have Alpha-1, emphysema will occur more frequently in the upper part of the lung. In those with Alpha-1 emphysema, the lower parts of the lung are most commonly affected. Bronchiectasis can occur in those with Alpha-1 lung disease. This is the permanent dilation and thickening of the bronchial tubes from chronic inflammation.

- **Pulmonary function tests.** Breathing tests that test for abnormal airflow are called pulmonary function tests (PFTs). In people with emphysema, the volume of air expelled from the lungs in one second (FEV1) will be diminished relative to the total amount of air expelled. Air can get out, but at a slower rate. People with emphysema will also tend to have hyper inflated lungs, and they will trap air in their lungs. This hyperinflation and air trapping tends to worsen with exercise. This is one reason that people with emphysema feel short of breath soon after starting exercise. Finally, complete PFTs measure how well the lungs can exchange oxygen (O<sub>2</sub>), which we want to get into our body. This is referred to as the diffusion capacity. When the small air sacs of the lung break down to form larger air sacs, or emphysema, the capacity of the lungs to exchange oxygen with the blood is impaired.

## What specialist should I see if I have Alpha-1 lung disease?

If you have any abnormal Alpha-1 genes (e.g., Z, S, F, null), discuss the risk of lung disease with your Alpha-1 doctor. Different Alpha-1 genes lead to different risk for disease. You may be referred to a pulmonologist who specializes in Alpha-1 lung disease.

## How does Alpha-1 lung disease affect other organs and systems in the body?

**Liver disease.** In addition to causing lung disease, 25 percent of people with Alpha-1 deficiency due to the PiZZ genes will develop liver disease. Liver disease from Alpha-1 can also affect newborns and children.

**Skin disease.** Panniculitis is a disorder of skin tissue, including fat that lies underneath the skin. It usually involves inflamed, red lumps, often found on the legs. This condition is very rare. Alpha-1 antitrypsin replacement therapy is effective for the treatment of skin lesions.

**Pulmonary hypertension.** This is a disorder of large and small blood vessels in the lung that leads to increased pressure, or hypertension, in the large vessels leading to the lungs from the right side of the heart. In very severe cases, the increasing pressure inside the right side of the heart can lead to right heart failure. This can be evaluated by cardiac ultrasound (cardiac echo) or heart catheterization.

**Hypoxemia.** Low oxygen levels in the bloodstream (hypoxemia) can be measured using a finger pulse oximeter. Severe emphysema and living at high altitude can be associated with hypoxemia and will require you to wear oxygen when walking, with sleep, or even 24 hours a day. Prolonged hypoxemia can cause pulmonary hypertension.

**Cachexia.** Significant weight loss, poor appetite, muscle atrophy and fatigue in someone who is not trying to lose weight is called cachexia. In people with Alpha-1, this condition is caused by the spillover of the inflammatory chemicals from the affected lung or liver into the main bloodstream and by the increasing amount of the body's energy that is devoted to the respiratory muscles.

**Deconditioning.** This is decreased ability to sustain a physical effort, from walking to carrying grocery bags. The diagnosis of deconditioning is based on your symptoms and completion of a cardiopulmonary exercise test ordered by your doctor.

**Cardiovascular disease.** Overlap with coronary artery disease and hypertension is common in people with Alpha-1. The shortness of breath, hypoxemia and deconditioning may be worse. All people with Alpha-1 may be screened for cardiac disease. Attention should be paid to medications prescribed for the treatment of both conditions, as several lung medications can worsen a heart condition, and some medications used to treat hypertension and angina can negatively affect the lung.

**Thromboembolic disease.** People with Alpha-1 can develop blood clots, especially in the veins of the calves and thighs, which later can migrate into the lung circulation and cause pulmonary embolism. Engorged and painful veins or acute severe shortness of breath are symptoms associated with this disease. Testing in a hospital setting is necessary to perform a leg ultrasound and chest computed tomography. Treatment with blood thinners is the usual treatment.

## **Infections.**

- Nontuberculous mycobacteria lung infection, also called NTM, MAC or MAI, may occur more often in people with Alpha-1, even in heterozygous people, such as PiMZ. Nontuberculous mycobacteria are organisms commonly found in water and soil that can cause a lung disease resembling tuberculosis, although not contagious. Nontuberculous mycobacteria are difficult to treat, and consultation with an infectious disease specialist is often helpful.
- People with Alpha-1 who have a catheter like a port or PICC line for weekly Alpha-1 antitrypsin augmentation therapy administration can develop catheter-related bloodstream infections with bacteria found commonly on the skin. Testing in a

hospital setting is necessary to collect blood cultures. It is recommended to remove the catheter while receiving antibiotic treatment and carefully reconsider placing a new catheter.

**Lung cancer.** There is some evidence that people with Alpha-1 Z or S genes may be at increased risk of developing lung cancer, even in the absence of exposure to cigarette smoke or asbestos, the two most common risk factors for lung cancer. A CT of the chest is a useful screening method for lung cancer.

## How is Alpha-1 Antitrypsin Deficiency managed?

People with Alpha-1 may live long, healthy lives without ever getting lung or liver problems from their Alpha-1. For those who develop emphysema or COPD, treatment starts with the same medications and therapies used for those who get COPD without Alpha-1. The medications include:

- Inhaled bronchodilators
- Combination medication
- Inhaled corticosteroids
- Medication to prevent COPD flare-ups

In addition, specific therapy has been available for Alpha-1 lung disease since 1987, a class of medicine called augmentation therapy. This medication augments the alpha-1 antitrypsin protein in the blood with normal alpha-1 antitrypsin from healthy plasma donors and is infused into an arm vein. The dose is adjusted based on body weight, and this treatment is given once a week. This therapy does not help people with liver disease due to Alpha-1. There are currently four brands of augmentation therapy approved in the U.S. They include:

- Prolastin®
- Aralast™
- Zemaira®
- Glassia®

In addition to medications, treatment includes:

- Avoiding infection
- Oxygen therapy for those with oxygen saturation levels below 89%
- Breathing Retraining
- Techniques to bring up mucus
- Pulmonary rehabilitation
- Surgery.

Surgery is a treatment option for Alpha-1, depending on the type and severity of disease. This could include:

- Lung transplant
- Lung volume reduction although often people with Alpha-1 lung disease are not good candidates for surgical lung volume reduction surgery.
- Liver transplantation may be an option for people severely affected by Alpha-1 liver disease.
- Healthy Lifestyle

A healthy lifestyle is important for everyone, including people with Alpha-1 and their caregivers: A healthy lifestyle includes:

- Regular exercise
- Giving up smoking and avoiding secondhand smoke. This is important in managing Alpha-1. Smoking can accelerate or speed the development of Alpha-1 related emphysema and shorten lifespan.
- Healthy eating

## How does Alpha-1 lung disease affect my life expectancy?

People who continue to smoke and have Alpha-1 lung disease, have an average life expectancy of about 60 years of age. People who quit smoking or never smoked and have Alpha-1, can still develop Alpha-1 lung disease but they have a better prognosis, and many will have similar life expectancy compared to those who don't have Alpha-1. It is important to discover whether you have Alpha-1 early in life, since this could affect your choice to smoke or not. Some advocate screening for the abnormal Alpha-1 antitrypsin genes at birth. Remember, people with Alpha-1 can live a full life.

## What does the future hold?

Alpha-1 Antitrypsin Deficiency is fairly common among inherited disorders. Research is constantly being done to develop new therapies.

Visit our website for more information about support groups, clinical trials and lifestyle information.

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