Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency is a genetic disease that can affect the liver and the lungs. It increases the risk of developing emphysema, as many people with this disease develop emphysema as early as their 30s. The disease can also lead to liver problems at birth or later in life, and can cause several other less common problems.

Alpha-1 antitrypsin is an important body enzyme. It protects the lungs from damage by another enzyme called elastase, and if it is absent or defective, the lungs are more susceptible to damage, which results in emphysema. Defective alpha-1 antitrypsin not only fails to protect the lungs, it can actually damage the liver.

The disease is one of the most common lethal genetic diseases in Caucasians, but because its symptoms can mimic ordinary asthma and emphysema, it is significantly underdiagnosed—many people do not know they have it.[1]

Other names:

Alpha-1 antitrypsin deficiency is sometimes written as α1-antitrypsin deficiency, with the Greek letter α. Common abbreviations include:

- AAT deficiency
- A1AD
- Alpha-1

Types

Alpha-1 antitrypsin is an enzyme, or protein, with an important job to do in the body. The instructions that code for enzymes like this one are called genes, and everyone gets one copy of every gene from each parent (with some exceptions that aren't important here). So everyone has two copies of each gene. The gene for the alpha-1 antitrypsin enzyme is called "Pi," which stands for protease inhibitor, and each person gets a copy of Pi from their mother and a copy from their father.
The different types of alpha-1 antitrypsin deficiency are based on how many copies of the Pi gene are defective—one, or both.
The normal gene that makes alpha-1 antitrypsin produces a type of alpha-1 antitrypsin called M. A normal person who doesn't have alpha-1 antitrypsin deficiency is referred to as type PiMM. "Pi" refers to the protease inhibitor system, and MM refers to the fact that two normal copies of the gene are producing two normal copies of alpha-1 antitrypsin, each called M.

PiZZ

The most common genetic defect that causes alpha-1 antitrypsin deficiency is the one that produces a type of alpha-1 antitrypsin called Z. Thus, the label of PiZZ refers to a person with two copies of a defective version of the gene, causing all of the antitrypsin that is made to be defective. (Technically, the Z refers to the defective antitrypsin and not to the gene itself.)

PiSZ

This form of alpha-1 antitrypsin deficiency is caused by one copy of a defective gene, Z, and one copy of a nearly normal gene, S. There is still plenty of functional alpha-1 antitrypsin that is made by the S copy. This type of deficiency has not been definitively known to cause disease, but it may be associated with the development of emphysema at a younger age in adulthood than would be expected.

Null genotype

In this type of disease, defective alpha-1 antitrypsin isn't made—in fact, no alpha-1 antitrypsin is made whatsoever. This may be caused by the absence of the gene or a defect in the gene severe enough to not let it function at all to produce any protein. This type is called Pi null/null, or the null genotype. (A genotype is a set of genetic information.) This type of alpha-1 antitrypsin deficiency has the typical lung problems but no liver problems, since defective alpha-1 antitrypsin hurts the liver, and in this disease there is no defective alpha-1 antitrypsin to cause that damage.

Carriers

Other types, such as PiMS or PiMZ, generally don't cause the disease. People with PiMZ are considered to be carriers of the disease, though. If both the mother and the father are carriers, then, on average, one-fourth of their children will have the full-blown disease. Carriers generally make about 40&–60% of the normal amount of alpha-1 antitrypsin. This quantity is sufficient to not cause any damage to the lungs and liver. However, there is some evidence that being a carrier increases the risk of lung [2] or liver cancer. [3]

Note on terminology

The terminology refers to the types of proteins detected by the blood test used to detect this disease. The actual gene itself is not detected. So, these types are technically phenotypes (which refers to an organism's characteristics), not genotypes (which refers to an organism's genes). (For more information on the difference between a genotype and a phenotype, click here (https://web.archive.org/web/20121026102657/http://en.wikipedia.org/wiki/Genotype-phenotype_distinction).

Signs and Symptoms

The most common signs and symptoms of alpha-1 antitrypsin deficiency are related to the **lung problems** that the deficiency causes, and include cough, wheezing, and increased sputum (phlegm). Unfortunately, most patients with emphysema from alpha-1 antitrypsin deficiency won't be diagnosed with the deficiency; their lung problems look too similar to common asthma or to emphysema caused by smoking. The fact that alpha-1 antitrypsin deficiency emphysema can improve somewhat with bronchodilators and inhaled steroids (both medications commonly used in asthma) further confuses the diagnosis. Poorly controlled asthma may be the first indication that a child in fact has alpha-1 antitrypsin deficiency. Likewise, because emphysema in these patients occurs at a relatively young age—in the thirties and forties, and sooner in people who smoke—an adult developing emphysema at a young age is often a strong clue to alpha-1 antitrypsin deficiency.

Other tip-offs include:

- **Neonatal hepatitis**: One of the earliest signs of alpha-1 antitrypsin deficiency is liver disease in a newborn, such as inflammation of the liver (hepatitis), enlarged liver (hepatomegaly), and jaundice. This occurs in only a minority of patients, though; only 20% of people with alpha-1 antitrypsin deficiency had liver problems causing jaundice as a newborn. At this early stage, there is very little else to indicate that the cause is alpha-1 antitrypsin deficiency, and the condition is indistinguishable from idiopathic neonatal hepatitis (liver inflammation of the newborn of unknown cause). Ten percent to 20% of cases of idiopathic neonatal hepatitis are eventually determined to be caused by alpha-1 antitrypsin deficiency.
- **Enlarged liver** (hepatomegaly). This can be caused by a variety of diseases, however.
- **Jaundice** (caused by blockage of the release of bilirubin into the blood). Jaundice can be caused by a great variety of diseases, however.
- **Liver failure**: Liver failure may occur in the newborn period, later in childhood, or in young adulthood due to cirrhosis. Alpha-1 antitrypsin deficiency is the leading cause of liver transplantation in the newborn.
- **Cirrhosis**: The liver problems that occur during the newborn period may go away on their own or they may worsen to the point of liver failure. Some patients with alpha-1 antitrypsin deficiency develop cirrhosis during adolescence and young adulthood. They eventually may require a liver transplant.
- **Growth failure**: Chronic lung disease or chronic liver disease may be subtle enough to go unnoticed, but may cause a child with alpha-1 antitrypsin deficiency to not grow as quickly. A decrease in growth velocity, or "falling off the growth curve," can sometimes be the first indication of an underlying chronic disease. Alpha-1 antitrypsin deficiency is one of the many diseases that a child would be tested for in cases of growth failure.
- **Pancreatitis**: In much the same way that antitrypsin protects the lungs from damage, antitrypsin also protects the pancreas from damage by protein-digesting enzymes. Individuals with alpha-1 antitrypsin deficiency have a higher risk of having pancreatitis. They may get recurrent pancreatitis.
- **Necrotizing panniculitis**: A very small number of people who have alpha-1 antitrypsin deficiency have a rare type of skin disease called necrotizing panniculitis. This skin disease can cause painful lumps under or on the surface of the skin.
- **Hyperresonant breath sounds**: An increased echo quality of the breath sounds when listening with a stethoscope can indicate that there is emphysema, as there is more air and less tissue in the lungs.
- **Increased diameter from back to chest (AP diameter):** This is another indication that there is too much air in the lungs, which can be seen in emphysema. This increased diameter may be noticed simply by examining the person in severe enough cases, but it is most clearly seen on the chest x-ray.
- **Liver appears to be enlarged (palpable liver edge)**: This is known as apparent hepatomegaly. This is caused by the liver being pushed downwards by the expansion of the lungs, caused by emphysema. Because one can feel the liver under the ribs, it seems to be enlarged. Also, the liver may in fact also be enlarged because of liver disease from alpha-1 antitrypsin deficiency.

Causes

Genetic cause

The term "alpha-1 antitrypsin deficiency" is a bit of a misnomer, because generally the problem isn't too little antitrypsin—it's defective antitrypsin. As mentioned above, alpha-1 antitrypsin deficiency is inherited. It is caused by having a defect in both copies of the gene that makes the protein alpha-1 antitrypsin. One copy is inherited from the father, and one copy is inherited from the mother. If both genes are missing or defective, then effective antitrypsin isn't produced.

Wrong shape

Generally, alpha-1 antitrypsin deficiency occurs when the alpha-1 antitrypsin proteins made in the liver are not the right shape. The alpha-1 antitrypsin gets stuck inside liver cells and can't get into the bloodstream to travel to the lungs. This leads to the two main manifestations of the disease: lung damage, because the protein isn't there to protect the lungs from the harmful enzyme elastase, and liver damage, because the proteins build up in the liver

where they don't belong. The exception to this rule is the null type of alpha-1 antitrypsin deficiency, in which no enzyme is made at all, not even the damaged version. The lungs are still at risk in the null type, but the liver isn't, because there is no enzyme buildup there.

Lung damage

Alpha-1 antitrypsin deficiency leads to lung damage because the faulty enzyme doesn't protect the lung from a destructive enzyme called **elastase**.
Antitrypsins are proteins that, as the name implies, block other enzymes called **trypsins**. Trypsins break down proteins, so antitrypsins prevent that breakdown. Antitrypsins can be found in the intestines, where they control digestion. Alpha-1 antitrypsin is made in the liver, then goes into the bloodstream and helps protect the body's organs from the harmful effects of other enzymes that break down proteins. One of the main organs it protects is the lungs.
The main lung enzyme that is blocked by alpha-1 antitrypsin is called elastase; it is another enzyme related to trypsin that breaks down proteins. Elastase isn't all bad. Its job is to break down foreign materials in the lungs, such as parts of bacteria, nicotine, environmental pollutants, and anything else that could cause damage.
The trouble arises when elastase begins breaking down the lung itself by eating away at the normal proteins in the lungs. This action of elastase is normally prevented by alpha-1 antitrypsin, but defective antitrypsin allows elastase to damage the lung. When enough protein is broken down, the lung tissue structure is broken and large pockets of air form within the lungs. This is emphysema, which can result in wheezing, shortness of breath, and difficulty breathing. Emphysema commonly occurs in long-time smokers over the age of 50. But if enphysema occurs before the age of 45, then the individual is highly likely to have alpha-1 antitrypsin deficiency. A particular type of emphysema that these patients are prone to is called panacinar emphysema.
In alpha-1 antitrypsin deficiency, the levels of antitrypsin are usually 10%–20% of normal.

Liver damage

When misshapen alpha-1 antitrypsin builds up in the liver, the liver can become enlarged, or can develop cirrhosis. Cirrhosis is a hardening deterioration of the liver which eventually leads to liver failure. The liver can also become blocked up and not allow bilirubin, a yellow pigmented breakdown product of blood, to be changed into a water-soluble form and be excreted from the body. The bilirubin can back up into in the blood, resulting in jaundice, a yellow tint of the skin. Jaundice of some types can be damaging to newborns. In extreme cases it can cause mental retardation and cerebral palsy, known as kernicterus.
The above liver problems can occur at birth or later in life. The liver problems that come with alpha-1 antitrypsin deficiency are caused by defective alpha-1 antitrypsin, and so liver problems are not seen in individuals with the complete absence of production by the alpha-1 antitrypsin gene (either due to absence of the gene or severe derangement of the gene).

Diagnosis

The diagnosis of alpha-1 antitrypsin deficiency isn't obvious; it must usually be suspected and searched for. **Unexplained hepatitis** in a newborn, **premature emphysema**, or **steadily worsening asthma** are some things that might prompt a doctor to test for alpha-1 antitrypsin deficiency.

Exams and tests

Testing is done mainly by determining the **type** of antitrypsin proteins in the body and by measuring the **level** of antitrypsin in the body.

Types of antitrypsin

As discussed above in Types, there are several forms of antitrypsin proteins a person could have. A normal person has "PiMM" type, while most alpha-1 antitrypsin patients have the "PiZZ" type. But there are many others.

Levels of antitrypsin

A direct level, or amount, of antitrypsin in the bloodstream is also measured. This test is done together with the above antitrypsin phenotype test. In fact, this test is done even if it is known that an individual has the PiZZ phenotype, since there are rare cases where an individual will have an abnormal type and yet still produce enough antitrypsin that he or she will not have any actual disease.

- **100%**: An alpha-1 antitrypsin level of close to 100% is normal, and if a person is sick for any reason, the levels may be higher than 100%. This is because alpha-1 antitrypsin is an acute phase reactant, or a body substance that increases when the person is stressed, sick, or has inflammation.
- **50%**: An alpha-1 antitrypsin level of about 50% indicates that the person is a carrier. They will not have any signs of disease. If a person is being evaluated for emphysema, lung problems, or liver problems, and an alpha-1 antitrypsin level is checked because alpha-1 antitrypsin deficiency is suspected, then a level of 50% may be surprising, but this level would be a coincidence and would not have anything to do with the underlying liver or lung disease. In fact, four percent of Caucasian Americans are carriers of alpha-1 antitrypsin deficiency, and so this scenario will occur about four percent of the time.
- **Less than 20%**: An alpha-1 antitrypsin level of less than 20% means that the person definitely has alpha-1 antitrypsin deficiency.

Pulmonary function tests

In cases of an unknown lung disease in children or young adults, or cases of poorly controlled asthma, a pulmonary function test (also known as a lung function test) can be performed to help make the diagnosis. While both asthma and emphysema will produce pulmonary function test results which show obstructive lung disease, asthma is reversible (it gets better with medication), while emphysema is irreversible. Emphysema improves somewhat with medication, but for the most part is categorized as irreversible, as is the closely-related disease COPD (chronic obstructive pulmonary disease).

Chest x-ray

A chest x-ray is performed in all children and adults when first diagnosing asthma, and a chest x-ray may be performed again if the patient is not getting better as expected. If a person with alpha-1 antitrypsin deficiency has already developed significant emphysema, a chest x-ray will show the following signs of hyperinflated lungs:

- Increased width of the chest from back to front
- Increased air seen in the lungs
- Flattening of the diaphragm (caused by hyperinflated lungs)

CT scan of the chest

This test is done to determine if there is damaged lung tissue caused by emphysema that can not be seen on chest x-ray. This test may be done when alpha-1 antitrypsin deficiency is suspected because of liver disease, or some problems other than lung disease, and the chest x-ray is normal. It can be used to monitor progression of the disease over years.[4]

Liver function test

Liver function tests are blood tests that determine the levels of liver enzymes, such as ALT, AST, and alkaline phosphate. Abnormally high levels mean inflammation of the liver of some kind.

Newborn screening

Alpha-1 antitrypsin is not tested for in newborn screening exams, including the expanded newborn screen such as the one used in Illinois and Texas. Newborns who have a family history of alpha-1 antitrypsin deficiency may specifically be screened.

Treatment

Treatments for alpha-1 antitrypsin deficiency include medications, enzyme replacement, surgery, and quitting smoking.

Medications

Danazol

Danazol, a drug related to **testosterone**, increases the production of alpha-1 antitrypsin. Unfortunately, it has masculinizing effects, so it is not suitable for women. It can cause long-term toxicity in men.

Liberal use of acetominophen

People with alpha-1 antitrypsin deficiency are instructed to take acetaminophen (Tylenol) when they are sick and have fevers, even if it is a minor illness and they otherwise would not take any meds. This is related to the fact that alpha-1 antitrypsin is an acute phase reactant, so its production is increased during illness and inflammation. If this increase is prevented, then this could prevent further accumulation of alpha-1 antitrypsin in the liver and could delay the onset of cirrhosis and liver failure.

Therapies

Enzyme replacement therapy

In enzyme replacement therapy, alpha-1 antitrypsin is isolated from human blood, then given intravenously. Brands include Aralast, Prolastin and Zemaira. This treatment is relatively new, so its long-term effectiveness and safety are still being evaluated.[5] Pure alpha-1 antitrypsin, produced by recombinant DNA technology (that is, produced in a laboratory directly from DNA and not taken from human blood), is also available for treatment. This medication can be given intravenously or in aerosolized form. It is extremely expensive, costing $20,000 to $30,000 per year.

Liver transplant

Because alpha-1 antitrypsin is made in the liver, a liver transplant is generally a cure for alpha-1 antitrypsin deficiency, although the lung damage that has already occurred is irreversible. Organ transplantation creates new risks, such as suppression of the immune system, so the decision must be carefully balanced for each patient.

Vaccines

Individuals with lung disease, such as emphysema, are more prone to pneumonia and the flu. More importantly, the damage that can occur in the lungs in alpha-1 antitrypsin deficiency can be triggered by inflammation from a bacterial or viral infection. So it is very important that these lung infections be avoided in people with alpha-1 antitrypsin deficiency. These patients should receive the **pneumococcal vaccine** ("pneumonia shot") and the **influenza vaccine** ("flu shot").

Treatment for emphysema

People with alpha-1 antitrypsin deficiency who have emphysema can be treated for their lung symptoms with **bronchodilators** (such as albuterol) and inhaled steroids. In more severe cases, patients may need to be on **chronic oxygen therapy**.

Holistic and alternative treatments

Avoidance of smoking

Cigarette smoke is especially harmful to individuals with alpha-1 antitrypsin deficiency. In addition to increasing the inflammatory reaction in the airways, and providing toxins which cause direct damage to the lungs, cigarette smoke directly inactivates whatever alpha 1-antitrypsin the person may still have. In people with alpha-1 antitrypsin deficiency, smoking can shorten the life expectancy by about 20 years. Emphysema starts 10 years sooner than in non-smokers with the disease.[6]

Research

Gene therapy involves introducing a normal copy of a defective gene by splicing into a virus and infecting the patient with that virus. Viruses often insert their own genetic material into a person's genetic material, so in this case the virus would insert a good copy of the alpha-1 antitrypsin gene. The gene would then lead to the production of alpha-1 antitrypsin that functions normally, thereby protecting the lung. Studies are being done to try this approach in alpha-1 antitrypsin deficiency.[7] [8]

Expected Outcome

In a minority of cases, patients have no symptoms of alpha-1 antitrypsin deficiency and live a nearly normal lifespan if there is no cigarette smoke exposure. There are a few people who may never know that they have alpha-1 antitrypsin deficiency, and some people who may not have any symptoms or problems except for developing emphysema in late adulthood.
Some people may have more severe liver and lung disease. In one study of 1,129 people with alpha-1 antitrypsin deficiency, about 3% died each year. [9]
People with alpha-1 antitrypsin deficiency have an increased risk of cancer, specifically lung cancer [10] and liver cancer. One study suggested that carriers have an increased risk of lung cancer[2], and there is evidence that liver cancer risk is increased in carriers as well.[3] It is now difficult to be sure what the length of lifespan and the quality of life will be for people who are now being diagnosed with alpha-1 antitrypsin deficiency, as there are new treatments now available which have not yet been fully explored in long-term studies. Furthermore, there are new, promising areas of research in genetic and stem-cell therapies for this disease which may prove to radically change the outcome of the lives of people with alpha-1 antitrypsin deficiency.

History

Alpha-1 antitrypsin deficiency was discovered in 1963 by Carl-Bertil Laurell at the University of Lund, Sweden. Laurell, along with a medical resident, Sten Eriksson, made the discovery after noting that the enzyme didn't show up on a protein-detector gel in 5 of 1500 patient samples. Three of these five patients were found to have developed emphysema at a young age.
The link with liver disease was made six years later, when Sharp and colleagues described alpha-1 antitrypsin deficiency in patients with cirrhosis.[11]

Epidemiology

Statistics

The disease affects about one per 3000–5000 adult Caucasians. Among Caucasians worldwide, an estimated 117 million people are carriers and 3.4 million people have the disease.[6]

Prevalence

People of northern European, Iberian (Spain/Portugal), and Saudi Arabian ancestry are at the highest risk for alpha-1 antitrypsin deficiency. Four percent of Caucasians are carriers of the disease, with one PiZ gene copy. Among Caucasians (the group with the highest risk), about 1 in 2000 to 1 in 4000 people have alpha-1 antitrypsin deficiency. Men and women are affected equally. Nonwhites are less commonly affected.
There may be additional people with alpha-1 antitrypsin deficiency who do not have any problems or symptoms and who are not diagnosed.
About 3% of all people diagnosed with COPD may have undetected alpha-1 antitrypsin deficiency.[6]

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External Links

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