Alpha-1 Antitrypsin Deficiency: Liver Disease

Who is at risk to develop Alpha-1 liver disease?

Alpha-1 liver disease may affect children and adults who have abnormal Alpha-1 antitrypsin genes. Keys to suspecting Alpha-1 liver disease can include family members with a history of Alpha-1 disease, emphysema, COPD or unexplained liver disease.

To develop Alpha-1 liver disease, a person needs to inherit one abnormal Alpha-1 antitrypsin gene (DNA material) from each parent. People with two Alpha-1 Z genes are at greatest risk of Alpha-1 liver disease, although other rarer Alpha-1 genes may increase the risk of liver disease. The risk of liver disease in Alpha-1 increases if the person suffers additional liver injury such as from viral infections (hepatitis A, B or C, or HIV infection), from alcohol abuse, from fat deposition within the liver (fatty liver), from occupational exposures to liver-toxic chemicals or from association with other genetic diseases (e.g., hemochromatosis).

If a person has one normal, M gene and one abnormal, Z gene, the risk to develop Alpha-1 liver disease is greatly reduced. If a person has two abnormal Z genes, there is a higher risk of Alpha-1 liver disease. One out of four people with ZZ Alpha-1 will develop liver disease at some point in their lifetime. The liver disease can be present at birth, and up to 5 percent of infants develop severe liver disease during the first year of life. After the first year of life, children are most commonly tested for Alpha-1 disease when they develop jaundice or elevations of their liver blood tests during other acute childhood illnesses. Rarely, the doctor may test an adult with elevated liver enzymes for Alpha-1 disease and establish a delayed diagnosis of ZZ Alpha-1.

Why do people with Alpha-1 develop liver disease?

Liver is the major site of Alpha-1 antitrypsin protein production. The hepatocytes (liver's structural cells) read the abnormal message encoded in their Z gene and produce the abnormal Z Alpha-1 antitrypsin protein.

This abnormal protein forms polymers (a chain of multiple Z protein molecules) that cannot leave the hepatocytes. Liver damage occurs when the hepatocytes become clogged with these polymers and die off. Lung damage associated with Alpha-1 is different. The lung tissue is deficient in Alpha-1 antitrypsin protein, because the protein trapped in the liver is unable to reach the lungs and other organs. It is "stuck" inside the liver's hepatocytes. For this reason, Alpha-1 antitrypsin augmentation therapy works for people with Alpha-1 lung disease but does not work for those with Alpha-1 liver disease.

What are the symptoms of adult Alpha-1 Liver disease?

Many people with Alpha-1 liver disease have no symptoms until late stages of the disease. When the liver damage reaches the most severe form, liver cirrhosis can occur. Cirrhosis is when the hepatocytes are

replaced with scar tissue. People with cirrhosis often experience:

- loss of appetite
- weakness, fatigue
- nausea
- abdominal pain
- weight loss
- skin discoloration (jaundice or yellowing of the skin)
- fluid accumulation under the skin (edema) or within the abdomen (ascites)
- bruising easily and abnormal bleeding, like nose or gastrointestinal bleeding

Other symptoms of severe liver disease can include sensitivity to certain medications cleared from the system via the liver, changes in personality and sleep habits, increased risk for infections and liver cancer.

What tests diagnose Alpha-1 liver disease?

Your doctor may have you do a number of tests to determine if you have Alpha-1 liver disease. These may include:

- Detailed medical history including family history of lung disease
- Physical exam
- Alpha-1 antitrypsin level and Alpha-1 phenotype or genotype in the blood
- Ultrasound or computed tomography of the liver to measure liver size, the blood flow within the liver and the echogenicity (Increased echogenicity means higher chance of scar formation, fatty accumulation or cirrhosis of the liver.)
- Biopsy or CT elastography to quantify the amount and distribution of the scar tissue in relationship to the other liver structures (hepatocytes, blood vessels, bile ducts)

People with Alpha-1 and one or two Z genes or other at-risk Alpha-1 genes with liver disease should be followed on an annual basis with:

- blood tests (liver panel, blood clotting tests, blood cell counts, renal function, tumor markers like alpha fetoprotein)
- liver ultrasound
- MELD score (a composite test based on blood test results) to determine the severity of liver disease

People with Alpha-1 with one Z gene and no liver disease should have a liver panel and liver ultrasound annually.

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

If you have any abnormal Alpha-1 genes (e.g., Z, S, F, null), you should discuss the risk of liver disease with your Alpha-1 doctor, based on your particular Alpha-1 inherited abnormality. If you have the Z Alpha-1 gene and abnormal liver tests, you will likely be referred to a hepatologist (liver specialist) or to a gastroenterologist with an interest in liver diseases. If you have cirrhosis and more advanced disease, you may be referred to a liver transplant center. Surgeons and transplant hepatologists will determine the eligibility for liver transplant, which is the only available cure for Alpha-1 liver disease.

How does Alpha-1 liver disease affect other organs and systems?

The liver is anatomically or physiologically connected to all the body's vital systems (e.g., brain, heart, kidneys).

Toxins in the blood and brain. Toxins build up in the blood and brain, because a cirrhotic liver is ineffective at removing them. Toxins can slow mental functioning and cause changes in personality, forgetfulness, trouble concentrating, neglect of personal appearance, changes in sleep habits, unresponsiveness, coma and even death.

Low blood pressure (hypotension). Hormones that dilate the systemic blood vessels and lower the blood pressure are present in higher concentrations in people with cirrhosis. They may experience lightheadedness and syncope (fainting). This condition will make the heart pump faster and stronger and eventually lead to heart failure.

High blood pressure in the pulmonary artery (pulmonary hypertension). This condition will lead to low oxygen saturations (hypoxemia) and difficulty breathing (dyspnea). A cardiac ultrasound can suggest the diagnosis. A right heart catheterization confirms it. Pulmonary hypertension is a severe complication of liver cirrhosis, and its diagnosis is a strong indication of the need for liver transplant.

Varices. A varix is an enlarged vein with thin walls that cannot handle high flow or elevated pressure without bursting easily. In cirrhosis, blood flow through the liver is blocked by scar tissue formation and backs up in veins of the stomach and esophagus, forming varices. When distended, these varices burst and can cause severe bleeding (a serious emergency that requires immediate medical attention).

Bruising and bleeding. The liver makes important clotting factors, proteins that help blood form clots. Therefore someone with Alpha-1 liver disease will bleed or bruise more easily, and for a longer period of time.

Edema and ascites. The protein albumin is produced in the liver. Albumin is important in bodily fluid regulation. As the liver loses its ability to make this protein, water accumulates in the abdomen (ascites) and legs (edema).

Sensitivity to medication. A cirrhotic liver filters certain medications (e.g., pain medications or sleeping aids) more slowly than a healthy liver. Therefore, the drugs stay active for longer than expected, build up in the system and can lead to side effects.

Liver cancer. The cancer arising from the hepatocytes is called hepatocellular carcinoma. It is a common cancer with high mortality in patients with cirrhosis from Alpha-1 liver disease.

Kidney failure. The systemic low blood pressure and the high pressure inside the abdomen due to ascites can make the kidneys lose their ability to efficiently filter the blood and concentrate urine.

Diabetes and hypoglycemia. Insulin is a hormone produced by the pancreas that helps regulate glucose (blood sugar) levels. The cirrhotic liver does not respond to insulin. Thus, glucose cannot enter the cells and stays elevated in the blood (diabetes). People with cirrhosis are not able to mobilize glucose out of the body's reserves, and they can easily develop low blood sugar (hypoglycemia).

What is the treatment for Alpha-1 liver disease?

The cirrhosis associated with adult Alpha-1 liver disease should be treated the same as cirrhosis of any cause. This includes treatments to monitor portal hypertension (elevated blood pressure in the circulation of the liver); monitoring and treatment of esophageal varices; adjustment of medication doses to account for changes in metabolism of drugs in an injured liver; and other measures. If the liver disease continues to worsen in spite of these measures, liver transplantation is the only potential cure.

Severe infant liver failure in Alpha-1 is always treated with liver transplantation, which cures the disease by replacing the failing liver with a liver that has normal Alpha-1 genes. A successful liver transplant leads to normal blood and lung levels of normal Alpha-1 antitrypsin protein. Liver transplant, in general, is a very successful procedure, but the availability of donor livers is outstripped by the demand. Sadly, some people who need a transplant may not be able to get one in time.

Children and adults diagnosed with one or two abnormal Z genes should be educated to avoid alcohol and medications or herbal products with liver toxicity. They should be tested for possible viral hepatitis viruses (A, B, C) and vaccinated accordingly.

Family members of people with one or two abnormal Z genes should receive genetic counseling, as an early

diagnosis of Alpha-1 liver disease in family members will have a significant effect on their prognosis.

People with cirrhosis may receive treatment with:

- vitamin supplements to help with clotting disorder and blood cell count
- diuretics to help with the fluid retention
- antibiotics to prevent infections of the ascites fluid or absorption of bacterial products from the gut
- propranolol (a medication)
- bands/clips (placed inside the esophagus through a mini surgical procedure) or TIPS (trans hepatic intraoral shunt, a surgical procedure) to help decrease the blood flow from the liver to the esophageal varices.

How does Alpha-1 liver disease affect my life expectancy?

If you have one Z Alpha-1 gene and no liver disease, you have a normal life expectancy. A quarter of people with two Z Alpha-1 genes will develop liver disease at some point in their lives. If the Alpha-1 liver disease progresses rapidly towards cirrhosis of the liver with complications, and you are not eligible for liver transplantations, then life expectancy can be greatly decreased.

More Information

To learn more about cirrhosis including causes of the disease and how it is diagnosed and treated, click on the links below.

- https://www.niddk.nih.gov/health-information/liver-disease/cirrhosis
- https://liverfoundation.org/

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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