Alpha1-antitrypsin deficiency (AATD)

European Reference Network on Hepatological Diseases (ERN RARE-LIVER)

https://rare-liver.eu **Contact: ern.rareliver@uke.de**

What is AATD?

Alpha1-antitrypsin deficiency (AATD) is an inborn genetic disorder. Severe AATD affects 1 in 2500 individuals, while mild AATD is more common. Due to an alteration in the DNA coding for the alpha1-antitrypsin protein (AAT), the otherwise soluble AAT sticks together, accumulates in the liver and is therefore decreased in the blood. Because AAT prevents the immune system from destroying lung tissue, AATD patients often develop lung emphysema, which leads to shortness of breath and reduced performance. The AAT accumulation in the liver results in liver damage and possibly fibrosis that could manifest from early childhood to a very advanced age. However, your doctor may be able to detect these processes earlier due to elevated liver enzymes or specialized ultrasound examinations.

Several mutations in the AAT gene can lead to AATD. The severe form is mostly caused by two simultaneously occurring PiZ mutations, termed the PiZZ genotype. Another common, less severe variant is called PiS. A combination of the non-mutated, so called M-variant with PiZ mutation cause only a mild AATD, termed PiMZ genotype.

Who is affected?

Individuals with severe AATD (such as the PiZZ genotype) can develop lung and liver disease spontaneously, while subjects with mild AATD typically require additional factors to develop a manifest disease.

Which symptoms can occur?

Lung disease only becomes apparent as shortness of breath in adults. Liver disease manifests at a very late stage in adults and it can present as fatigue, fluid retention in the belly (ascites), jaundice and/or vomiting of blood. In children, disease may present as jaundice in newborns associated with pale stools and dark urine, or as a large liver or spleen in childhood.

How is AATD diagnosed?

AATD diagnosis is made from the blood. First, the AAT level is measured and if diminished, a combination of a more specialized protein analysis and a genetic assessment can be performed.

A lung function test is used as a basic evaluation of lung status. A CT scan of the lung may yield useful additional insights.

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In clinical routine, liver involvement is assessed through liver enzyme measurements. A conventional ultrasound examination can detect/rule out advanced liver scaring and/or presence of liver tumors. A liver biopsy or specialized liver stiffness measurements can more accurately determine the stage of the liver disease. Liver biopsy might be useful in individuals with recurrently elevated liver enzymes in order to exclude additional liver diseases.

What are the complications of AATD?

Development of advanced chronic obstructive pulmonary disease (COPD), emphysema with shortness of breath, need for bronchodilatory inhalative treatment and later on for oxygen support. Development of end-stage liver disease with fatigue, fluid retention in the belly, development of liver cancer, risk of digestive bleeding etc.

Will my liver function be affected?

About 10-15% of adults with severe AATD develop an advanced liver fibrosis/liver cirrhosis with deteriorating liver functions, whereas it is affected in 2-3% of children.

What can my doctor do?

Concerning the liver disease, the management is primarily preventive (limited alcohol consumption, avoidance of obesity, viral hepatic infections and liver-damaging drugs). A treatment with ursodeoxycholic acid can be attempted, but was only systematically studied in children. The participation in ongoing clinical studies should be considered. In case of liver cirrhosis, a regular follow-up by an experienced hepatologist is recommended to manage possible complications and to evaluate the possibility of a liver transplantation.

The pulmonary disease requires specialized pulmonologist care. In addition to the treatment of chronic obstructive pulmonary disease/and or emphysema (bronchodilators, oxygen), it may require an intravenous augmentation with alpha1-antitrypsin and lung transplantation in advanced disease.

Do I need medical checkups?

There are no consented guidelines, but we recommended liver enzyme measurements at least once a year in addition to regular ultrasound and liver fibrosis evaluation for adults with severe AATD. In children with severe AATD, follow-up may be closer during the first months to check for growth.

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If you present pulmonary symptoms, regular follow-up with your pulmonologist is necessary. Functional tests to follow up your respiratory capacity will be proposed.

What can I do?

Medication: Weekly infusions of purified alpha1-antitrypsin (AAT) are used as a treatment of AATD-associated lung disease, whereas liver transplantation is the only curative treatment for AATD-related end-stage liver disease. Several promising therapeutic approaches are currently in clinical trials.

Diet: There is no specific diet recommended for AATD, but it is advisable to stay physically active and to maintain a healthy lifestyle with a balanced diet. There are special, AATD-independent dietary recommendations for individuals with liver cirrhosis, and for infants with neonatal cholestasis.

Do my family and I need to be genetically tested?

Given that AATD is an inherited disease, family screening is needed to evaluate individual risks.

Family planning:

Since AATD is a genetic disease, your partner will need to be screened to evaluate your risks of having offspring with mild/severe AATD. If a child is diagnosed, a screening of siblings and parents should be considered.

How can I find a specialist?

The European Reference Network on Hepatological Diseases (ERN RARE-LIVER) can help you to find a specialist in your country. To find information and patient support, click on the section “patients” on the ERN RARE-LIVER website (https://rare-liver.eu/). Alternatively, you can contact the coordinating center for AATD-related liver disease directly (alpha1@ukaachen.de).

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