

## Alpha-1 antitrypsin deficiency and the liver

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The ADAPT Project, Queen Elizabeth Hospital Birmingham

Many patients who come to ADAPT are surprised when we explain to them that the vast majority of alpha-1 antitrypsin is actually made in the liver. In addition, people with alpha-1 antitrypsin deficiency do make a normal amount of alpha-1 antitrypsin protein but the problem arises because the alpha-1 antitrypsin produced is the wrong shape. In people who do not have alpha-1 antitrypsin deficiency, the normal alpha-1 antitrypsin protein is made in the liver, as shown in figure 1. It then enters the bloodstream and travels to the lung to protect it from developing emphysema. The problem for people with alpha-1 antitrypsin deficiency is that the alpha-1 antitrypsin gene is abnormal. As genes are the body's 'instructions' for making proteins, the alpha-1 antitrypsin protein is then made incorrectly. These abnormal alpha-1 antitrypsin proteins have a tendency to stick to each other and form a big chain, known as a polymer. The polymers are too big to get out of the liver cells and in to the blood stream, and this has 2 consequences. Firstly, most alpha-1 antitrypsin protein cannot get to the lung to protect it from emphysema, and secondly, the polymers that are trapped inside the liver cells can sometimes cause liver disease.

Several different types of liver conditions can be associated with alpha-1 antitrypsin deficiency. A Swedish study has been the most informative in terms of assessing the risk of developing childhood liver conditions. In the study a test was performed for alpha-1 antitrypsin deficiency in 200 000 infants born between 1972 and 1974. They found that 127 had the Z type of alpha-1 antitrypsin deficiency, and these subjects have been followed up every few years to check if they have developed liver or lung disease.

The study found that 14 babies (11%) developed jaundice shortly after birth (neonatal cholestasis) and a further 8 (6%) had other signs of liver disease. Of the 14 who developed jaundice, 3 went on to get liver cirrhosis between the ages of 2 & 4, but the rest of the babies who had jaundice or had other signs of liver disease got better.

Liver cirrhosis is a condition where the liver becomes permanently scarred and does not function well. Figure 2 shows a normal liver, which is smooth and shiny, and figure 3 shows a liver with cirrhosis that is rough and lumpy. The liver has 2 main functions — to make things and to get rid of things from the body. The liver makes blood clotting factors, proteins, sugar and bile, which helps with digestion of fats. The liver helps to get rid of hormones, waste products, alcohol and some drugs from the body.

informative as the Swedish study in children. Many have centred around post-mortem findings, with 15-20% of people with alpha-1 antitrypsin deficiency who died in their 50s, having liver cirrhosis. This figure increases to 40-45% of patients in their 60s. However, this is not an accurate way of assessing the risk of developing liver disease in people who attend ADAPT. The main reason for this is that post mortem studies are only done when the patient has died and liver cirrhosis may have

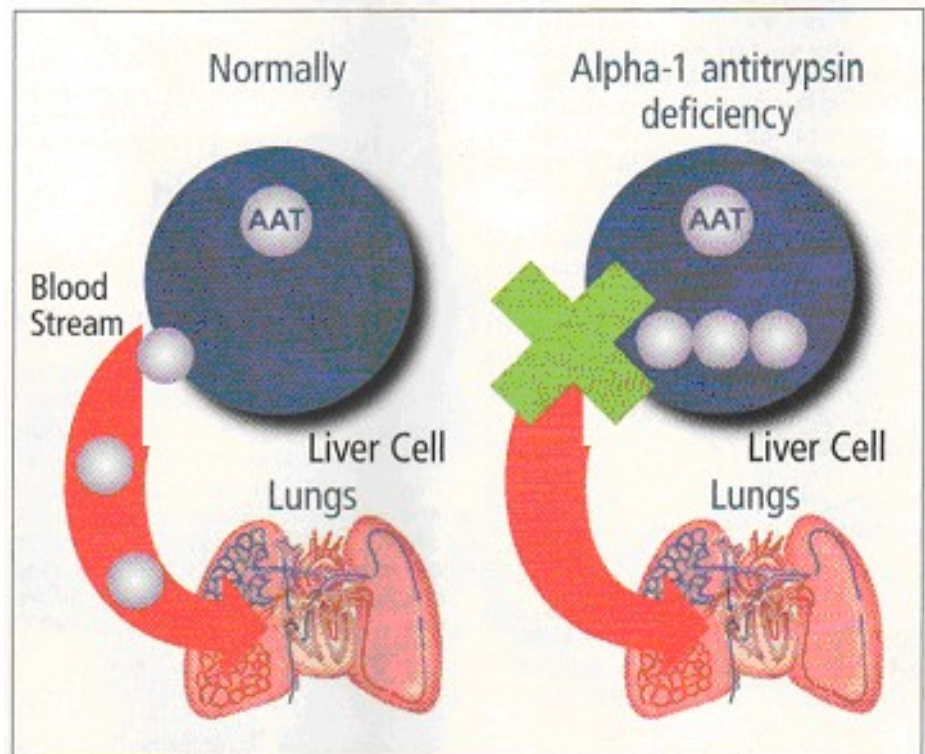


Figure 1

Therefore, if the liver is not working properly, patients can develop problems like bruising and bleeding (especially from the intestine), swelling of the legs and tummy associated with low protein levels, and problems with the sugar level being too low. Other symptoms can include the loss of body hair and the development of breasts and shrinking of the testicles in men (because the liver is not getting rid of hormones as it should). Itching and confusion caused by waste products being retained in the skin and the brain can also occur. You may recall that we sometimes ask you about these things in one of the questionnaires when you come to ADAPT.

Sometimes older adults can develop liver cirrhosis as well as children. The studies that look at this are not as

contributed to the death in many of these patients, so the numbers seen at post-mortem are probably falsely high. In addition, we know that only 1-2 % of adults who attend ADAPT have clinical signs and symptoms of liver cirrhosis, and this may be a more accurate estimation for people with alpha-1 antitrypsin deficiency who are alive now.

At ADAPT we check liver function blood tests at each visit. We have found that one particular blood test called gamma glutamyl transferase (GGT) is abnormal in around 27% of patients, despite only 1- 2% having liver cirrhosis. We know that drinking alcohol can cause this blood test to become abnormal, and we may have recommended that you reduce your alcohol intake if we have found this abnormality in your blood tests previously. However, we have also

done some new research over the last year and discovered that this blood test also relates to the severity of lung disease, and it may be lung disease that has caused this abnormality in some patients. We measure 3 other liver blood tests at each visit to ADAPT, and these tend to be abnormal in a much smaller proportion of patients (2-5%).

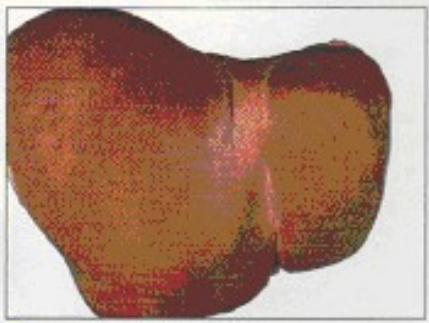


Figure 2

In order to reduce the risk of getting liver cirrhosis, it is recommended that people with alpha-1 antitrypsin deficiency drink up to, but no more than the maximum the government recommends. This is currently 14 units per week for women and 21 units per week for men, with one

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unit corresponding to a small glass of normal strength wine, half a pint of beer or a single measure of spirits. If somebody with alpha-1 antitrypsin deficiency has liver cirrhosis, it is best not to drink alcohol at all and vaccinations against the other liver diseases, hepatitis B and C, are recommended. Some of the symptoms caused by liver cirrhosis can be treated with various types of medication, but the only 'cure' as the liver gives up is a liver transplant. Incidentally, having a liver transplant will also 'cure' alpha-1 antitrypsin deficiency, because the new liver will have normal genes. These will give instructions to make normal alpha-1 antitrypsin proteins, which will not form polymers, and will be able to get into the blood stream and to the lungs, to protect them from emphysema. However, a liver transplant is a huge operation, and there is a shortage of donated organs so it is only reserved for patients with little liver function left. In addition, having a liver transplant will not repair any damage that may have occurred in the lung prior to the surgery. Therefore, liver transplant cannot, unfortunately, provide a 'cure' for alpha-1 antitrypsin deficiency for everyone.

There are, however, new medications being developed to try to stop the abnormal alpha-1 antitrypsin proteins joining together to form the polymers that cause the underlying problems. Work is also taking place at ADAPT, to insert a normal 'M' gene into the DNA of patients with alpha-1 antitrypsin deficiency. If this can eventually be



Figure 3

made successful in liver cells, the correct 'instructions' will be available and the normal alpha-1 antitrypsin protein should be made, providing a cure for alpha-1 antitrypsin deficiency.