



The Childhood Liver Disease Research and Education Network strives to provide information and support to individuals and families affected by liver disease through its many research programs.

BILE ACID SYNTHESIS AND METABOLISM DEFECTS

What are bile acid defects (inborn errors of bile acid metabolism)?

Bile acids are chemicals made by the liver and put into bile, the yellow fluid that flows from the liver to the intestines. Bile acids are the body's natural detergents that help the intestine break down and use the fat and vitamins from the foods we eat. Bile acids are made from cholesterol. There are many steps in the process of making bile acids, and each step needs a certain "enzyme." An enzyme is a protein that causes something to happen in the body. If each step of the process is not completed correctly, the bile acids are not made correctly. The result is that the person's body cannot make bile normally and the intestine cannot absorb and use fats and vitamins correctly. Some people are born with genes inherited from their parents that do not make normal enzymes. This is called a birth defect or an "inborn error", which means there is problem with a normal body function that has been there since birth. Most birth defects happen because a patient has inherited defective genes from his or her parents. Bile acid defects cause liver disease. They can also be part of other diseases, like diseases of the brain and nervous system.

How do you get a bile acid defect?

Bile acid defects are inherited, which means they are caused by changes in genes that are passed on from parents to their children. Genes are codes in the cells of our body that control how proteins (enzymes) are made. There are a number of genes that are needed for all of the steps of the process of making bile acids. If all of these steps are completed correctly, the liver makes normal bile acids. Right now, doctors think there are about 17 steps in the process of making bile acids. Changes in genes can cause mistakes to happen at any one of these steps. In all of these defects, a person must inherit two changed genes, one from each parent. Changed genes that are inherited from both parents are called "autosomal recessive." When a parent has only one changed gene, it does not cause any problems. Patients who have inherited the changed gene from both parents will not be able to make bile acids correctly. This means their livers will not work correctly and they will get liver disease. Depending on which enzyme doesn't work correctly, the liver disease can vary from mild to severe.

Some patients have conditions called "peroxisomal" diseases. A peroxisome is an important part of a normal body cell like the nucleus or mitochondria. Two of the most common peroxisomal diseases are called Zellweger Disease and Neonatal



Adrenoleukodystrophy. In these two diseases, the patient has defects in the process of making bile acids because some of the steps occur within the peroxisome part of the cell. These diseases affect many organs in the body. This is because peroxisomes occur in cells throughout the body. In peroxisomal diseases, the liver disease can vary in severity. These diseases can also include problems in the brain, including mental retardation, convulsions, deafness, blindness, and muscle weakness.

What causes liver disease in bile acid defects?

There are two main ways the liver gets hurt in bile acid defects. The first happens when the liver is unable to make "normal" bile acids. Normal bile acids help to move bile through and out of the liver. This helps remove "waste" substances that can hurt the liver. When bile does not move out of the liver normally, toxins, drugs and other materials get trapped in the liver and damage it. The second way the liver gets hurt is by the chemicals that form from the abnormal bile acids. Doctors believe that both of these problems cause liver damage in people with bile acid defects.

What are the symptoms of liver disease in bile acid defects?

Symptoms of bile acid defects include:

- jaundice (eyes and skin turning yellow)
- poor growth
- liver or spleen enlargement
- bleeding
- rickets (vitamin D deficiency)
- liver disease of unknown cause
- abnormal blood tests to check how well the liver is working (liver function tests)
- amounts of vitamins in the blood may be lower than they should be

How are bile acid defects diagnosed?

Bile acid defects do not happen very often. Since bile acid defects are rare and can cause a variety of symptoms, these diseases may not be looked for when a patient is first seen. But if other causes of liver disease are not found, the doctor may send tests to look for bile acid defects. This usually includes tests on urine and blood to look for abnormal bile acids. These tests are done in only a few laboratories and may take some time to get the results back.



How is the liver disease treated in patients with bile acid defects?

The main goal in treating bile acid defects is to get the liver to work correctly again. The first thing that is done is helping the liver to make normal bile. The second step is to get rid of the poisons that build up in the liver. If these are successful, the liver can stay healthy. Right now, one of the best ways doctors have to treat bile acid defects is to give the patient natural bile acids. One of these, called cholic acid, is available for use in humans, but only as an investigational drug. This means it is being tested by doctors to see how well it works. It is not approved for use by the Food and Drug Administration (FDA) and cannot be written as a prescription by your doctor. Another bile acid, ursodeoxycholic acid, is a drug approved by the FDA for use in adults, but not for use in infants and children with liver disease. It may be prescribed by doctors for children as an "off-label indication." This means that this drug was approved by the FDA for a specific purpose, but it may be used for other reasons if the patient's doctor thinks it may help.

When first diagnosed, most patients with bile acid defects cannot digest and use fat in the diet and fat-soluble vitamins (vitamins A, D, E and K) correctly. There are special infant formulas that doctors can recommend to help the patient get enough nutrients. These formulas have fats and vitamins that are easier for the body to absorb. Some patients also need to take extra vitamins. Most patients who are treated with bile acids end up with normal blood tests of liver function and the liver is healthy. However, even with this treatment, the liver disease may get worse in some patients and cause severe scarring in the liver (called cirrhosis). If this happens, the patient may need a liver transplant. A liver transplant is a surgery that removes the sick liver and replaces it with a healthy one from another person.

What is the outlook for patients with bile acid defects?

When patients are treated with bile acids (cholic acid and ursodeoxycholic acid), most of their liver problems are corrected. These include jaundice, poor growth, poor use of fat and vitamins by the liver, and most blood tests of liver function. These improvements occur within several weeks of starting treatment. Patients need to continue to take the bile acids to prevent the liver from getting damaged. The bile acids usually have very few side effects. With this treatment, these patients can live a normal life. Sometimes, liver disease gets worse, even with treatment. In some patients, scarring in the liver continues to get worse and in some patients the liver quits working. These patients may need a liver transplant.



The livers of patients who are not treated with bile acids will become more damaged until scarring develops. If the scarring becomes severe and the liver stops working, the patient may need a liver transplant. This means the diseased liver is removed and replaced with a healthy liver from another person. When the body gets the new liver, it can tell that the new liver is not its own, and it tries to reject it. Doctors can give medicine to stop the body from rejecting the new liver, which must be taken for the rest of the patient's life.