



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.

## MITOCHONDRIAL HEPATOPATHIES

### What is a mitochondrial liver disease?

"Mitochondria" are the little "power plants" inside each cell of our bodies. They supply the cell with energy (called ATP). They do this by turning the fats, sugars and proteins we eat into energy. Cells need energy in order to do their normal functions. There are up to 2,000 mitochondria in each cell. If the mitochondria in a certain group of cells are not working well, the organ containing those cells does not get enough energy. This means that organ may not work well. "Hepatopathy" means a problem or disease in the liver. So, mitochondrial liver diseases are a special group of diseases of the liver. In this group of diseases, there is a problem with the way mitochondria are working. This leads to damage or poor function of the liver.

There are a number of other organs in the body that need quite a bit of energy to work well. These include the brain and the nervous system, the muscles, the heart, and the kidneys. Poorly working mitochondria may also affect these other organs. So, diseases of the mitochondria may affect a number of different organs at the same time or over time.

There are two main types of mitochondrial liver diseases. In "respiratory chain disorders," the mitochondria don't make enough energy. This is because the tools in the mitochondria did not form completely and are not able to do their job correctly. In "fatty acid oxidation defects," the mitochondria are unable to turn fats into energy. Mitochondria need several "enzymes" (proteins) to change fat into energy. In this type of disorder, the mitochondria are missing some of those enzymes. This means they can't turn the fats we eat into energy.

### What are the symptoms of liver disease in mitochondrial liver diseases?

Mitochondrial liver diseases can affect children of all ages and adults. Usually, a child suddenly becomes ill and shows several signs of liver disease such as:

- jaundice (yellow color of the skin and eyes)
- vomiting
- weakness
- low blood sugar levels and sleepiness
- elevated liver blood tests
- an increased amount of lactic acid in the blood



Sometimes, a doctor may be able to feel that the child's liver is larger than it should be. Usually, this means the liver contains extra fat or scar tissue. Sometimes, the first sign of a problem in the liver is when the liver suddenly and quickly quits performing its normal functions. This is called acute liver failure. Most children with acute liver failure caused by a mitochondrial problem will also have symptoms showing that another organ in the body is also sick. Usually, those organs aren't working correctly because they don't have enough energy. Common signs that the liver and other organs aren't working correctly include:

- Low muscle tone or weakness
- delayed development of motor skills
- convulsions (fits)
- slow movement of the intestines causing swollen abdomen or constipation

Sometimes there are also other signs, such as:

- anemia
- deafness
- sugar diabetes
- problems in the heart

### **How do you get a mitochondrial liver disease?**

There are two ways children can "inherit" mitochondrial liver diseases. One way is for the disease to be passed from parents to children through genes that are found on chromosomes, the genetic material in the nucleus of each cell in our body. Genes are codes that guide how each part of the body is made. Each person receives two genes for each trait in their body: one gene from the mother and one from the father. For the child to get one of these diseases, they must receive two changed genes (mutations), one from the mother and one from the father. It is common for people to have only one changed gene. These people are called "carriers." Usually, carriers do not get the disease that occurs in people with two changed genes. This means that parents of children with these diseases usually have no liver problems or other medical problems that could be caused by the single changed gene. This also explains why the risk to inherit two changed genes and to develop the disease will be increased if the parents are related to each other.

The other way these diseases may be passed from parents to children is through genes that are found in the mitochondria themselves. People receive all of the mitochondria in their cells from their mothers. Each mitochondrion has its own set of genes, but mitochondria have far fewer genes than chromosomes. Some mitochondrial diseases are caused by changes in mitochondrial genes. These genes are passed from the mother's mitochondria to the child. Usually, only relatives on the mother's side of the



family have a risk for being affected by these diseases. When the disease is passed from mitochondrial genes, other organs may also be involved, including the brain and nerves, eyes, hearing and the heart.

### **What happens to the liver in mitochondrial liver diseases?**

The liver is one of the largest organs in your body. It is found in the upper right part of your abdomen. It is very important to your health because it cleans your blood and helps fight infections. The liver stores vitamins, sugars, fats and other nutrients from the foods you eat. The liver makes many substances for your body. It also breaks down alcohol, drugs and other toxic substances that can hurt your body. The liver also removes a yellow substance from the body, called bilirubin, which builds up in the blood in many liver diseases. The term "liver disease" means a number of conditions that stop the liver from working as well as it should.

In mitochondrial liver diseases, the mitochondria do not make enough energy for the liver cells. This happens because the tools in the mitochondria did not develop normally. When the liver cells don't have enough energy, several problems can occur:

1. The liver can make too much lactic acid that can go into the blood. When people have too much lactic acid in their blood, they feel weak, lose their appetites and feel like vomiting.
2. Fat can collect in the liver cells. This can cause scarring of the liver in some patients. A large amount of scarring in the liver can cause the liver to quit performing its normal functions. This condition is called "cirrhosis."
3. Sometimes, the liver does not make enough sugar (glucose) for the rest of the body. This can hurt the brain and cause convulsions, sleepiness or unconsciousness.
4. Since the liver normally makes substances that help the blood clot, there may be increased bleeding in mitochondrial liver diseases

The amount of damage to the liver may vary from mild to severe in different patients. Each person is affected differently.

### **How are mitochondrial diseases found and diagnosed?**

First, the patient is checked by a health professional who knows about mitochondrial liver diseases. The doctor or nurse will ask many questions to learn about any medical problems the patient has had in the past. They will also ask about any medical problems in other members of the patient's family. The doctor will also do a complete physical



examination. The doctor will usually order an ultrasound test of the liver (this is like an x-ray). The doctor will also collect samples of the patient's blood, urine and tissues to be tested in a laboratory. The results of these tests help the doctor figure out the cause of the liver disease and if this is a mitochondrial liver disease. Most hospitals do not have a laboratory for these special tests, so they will send the samples to other specialized laboratories. This means it may take longer to get the results. Sometimes, it is not necessary to do all these tests. The doctor will decide which tests to do for each patient.

Tests on blood and urine are the first steps in figuring out how sick the liver is. They also help figure out if the mitochondria are not working correctly to make energy for the cells. The lab uses the blood sample to check many things:

- How well the liver is working
- The amount of glucose (sugar) in the blood
- The amount of ammonia in the blood
- The salt balance of the blood
- The amount of acid in the blood
- The amount of lactic acid in the blood
- The amount of pyruvate (another type of acid) in the blood
- The amount of ketone bodies (more acids) in the blood
- How well the blood clots
- A count of each type of blood cell

If the results of these lab tests show that there may be a mitochondrial disease, the lab will do more tests on the blood and urine samples. The additional tests will help them figure out if the patient has a fatty oxidation defect.

Still more tests may be needed to find the cause of the mitochondrial problem. In addition, if the results of the lab tests were normal but the doctor has other reasons to think there might be a mitochondrial disease, more tests will be taken. These can include:

- Testing for changes (mutations) in genes in the mitochondria and chromosomes in blood cells
- Looking at a sample of liver or muscle tissue (this sample is called a biopsy) under the microscope
- Measuring how well the mitochondria make energy in a sample of liver or muscle tissue, or in cells grown from a sample of skin tissue
- Getting a sample of the liquid around the spinal cord (this test is called a "spinal tap")

Because there are new causes of mitochondrial liver diseases discovered each year, new diagnostic tests may become available in the future.



## **How is liver disease treated in people with mitochondrial liver diseases?**

Right now, there is no cure for mitochondrial liver diseases. But there are some treatments for a number of the diseases. The patient's doctor is the best person to ask about which treatments might work for them. For some of the diseases, doctors might try to treat the patient with a variety of vitamins, antioxidants and mitochondrial co-factors, but this type of treatment has not been proven to work well. Some medicines that could damage mitochondria need to be avoided or stopped. With fatty acid oxidation defects, patients can do several things to help prevent episodes of sickness, such as:

- Don't go for too long without food
- Don't eat too many fatty foods
- Use certain medications recommended by the doctor

The doctor will help the patient learn more about each of these steps. If the mitochondrial disease is only in the liver and is severe and life-threatening, the doctor might recommend that the patient have a liver transplant. This means the damaged liver would be removed and replaced with a healthy one from another person. If the mitochondrial disease involves other organs (particularly the brain, muscles or heart), liver transplant will probably not help the patient and is not recommended.

There is a need for new treatments that will:

- help the mitochondria make more energy
- replace damaged mitochondria with healthy ones
- replace changed genes with normal genes

New treatments like these would have to help the liver. They would also have to help the other organs (like the brain) that are also hurt by mitochondrial diseases in some patients. New treatments like these are the subject of current research studies.

## **What is the outlook for someone with mitochondrial diseases?**

There is wide variation in how sick people get from mitochondrial diseases. Some patients have serious problems if the brain or heart is affected, or if the liver is severely affected. Some patients, especially babies, may die at a young age from a severe respiratory chain defect or fatty acid oxidation defect. But there are also patients who have only minor problems. Some people have only mild, manageable symptoms of liver disease or problems with other organs. Some people don't have problems with other organs at all. So, it is best to talk with your doctor to figure out how your diseases might turn out.



## **How can I learn more about mitochondrial liver diseases and pediatric liver diseases?**

- Ask your healthcare provider
- Access information available on-line
- Contact local, national or federal organizations and agencies dedicated to liver disease and/or mitochondrial diseases