



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.

PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC)

What is Progressive Familial Intrahepatic Cholestasis (PFIC)?

The name PFIC was coined in the early 1980's to describe a form of liver disease that primarily affects children. Taken word for word, it means: Progressive: tending to get worse over time; Familial: passed down to a child from the parents by way of the genes; Intrahepatic: involves disease inside the liver and not the bile ducts outside the liver; Cholestasis: means poor bile flow and build-up of substances in the liver that would normally be carried out of the liver into bile.

A number of medical terms have been used to describe PFIC patients. "Byler's disease" was used for Amish children with PFIC, in whom "PFIC" was first identified. Three types of PFIC have been labeled as PFIC-1, PFIC-2 and PFIC-3, although since we now understand these conditions at a genetic level, these terms are being used less and less. In recent years, it has been discovered that many patients with PFIC have mutations in one of three genes named *ATP8B1*, *ABCB11*, and *ABCB4*. These genes encode three proteins: *ATP8B1* encodes FIC1, *ABCB11* encodes BSEP, and *ABCB4* encodes MDR3. Mutations in these genes lead to a failure to make normal versions of these proteins and thereby cause PFIC in many patients. As a result, we think of PFIC as a family of diseases that look very similar but have different genetic causes. Thus PFIC-1 is referred to as FIC1 (familial intrahepatic cholestasis 1) deficiency or *ATP8B1* deficiency, PFIC-2 is referred to as BSEP (bile salt export pump) deficiency or *ABCB11* deficiency, and PFIC-3 as MDR3 (multidrug resistance-associated protein 3) deficiency or *ABCB4* deficiency. There is a wide variety of specific genetic mutations that lead to these diseases. Mutations that lead to a protein that is not formed or does not function results in severe disease. There are mutations that lead to partially functional proteins and in general the disease associated with these mutations is milder and some can even be intermittent in nature. The intermittent forms of this disease are often referred to as BRIC, which stands for benign recurrent intrahepatic cholestasis. Most of the subsequent discussion pertains to individuals with severe disease, referred in general as PFIC.

What are the symptoms of PFIC?

Patients with FIC1 or BSEP deficiency have similar symptoms; together they are called low-GGT PFIC because of a blood test result (GGT) that is low or normal rather than high as in most other forms of cholestasis. These diseases cause cholestasis that



begins in early childhood, with the average age at onset being 3 months. However, some patients whose genetic mutation is milder do not get symptoms of cholestasis until they are teenagers or young adults. The severe forms of these diseases can progress quickly leading to extensive scarring of the liver (cirrhosis) in the first years of life, while the milder forms can progress more slowly with minimal scarring even into the teenage years. Few patients with severe forms of disease have survived beyond 20 years without treatment.

Itching (pruritus) is the main symptom of cholestasis in many patients. Pruritus is often out of proportion to the level of jaundice (yellow eyes or skin), which is often low-grade and can wax and wane. Pruritus may be hard to identify in young babies because they lack the ability to scratch. Instead, they may be irritable and sleep poorly. Scratching starts as digging at the ears and eyes, which are the first areas to show bleeding and scarring. The itching may be very disabling and does not usually respond to medications. The scratching interferes with normal activities and sleep and may therefore hinder learning and schoolwork.

Problems with growth are another major feature of PFIC. Many patients are short for their age, but they may not be thin. Delays in puberty and in sexual development are common. Patients who are treated can have normal sexual development and several have given birth to normal children. Learning and school performance is normal in most patients receiving effective treatment, but is often delayed before treatment, probably as a result of the effects of constant scratching and its effects on sleep and attention in school.

Fat-soluble vitamin (A, E, D and K) deficiencies are common in untreated patients. Vitamin A deficiency can lead to problems with vision. Vitamin E deficiency can lead to problems with balance, strength and coordination. Vitamin D deficiency can lead to poor bone formation and an increased risk of broken bones. Vitamin K deficiency can lead to bleeding problems, which can be very dangerous especially if the bleeding occurs in the brain. For these reasons, most patients need extra vitamins. For some patients taking a special kind of Vitamin E (TPGS Vitamin E) can help with the absorption of all of the fat-soluble vitamins. Up to a third of patients have gallstones. Many patients have an enlarged liver or enlarged spleen.

Although patients with BSEP deficiency and patients with FIC1 deficiency are similar, there are differences between them. FIC1 deficiency, unlike BSEP deficiency, can affect many organs in the body including, the pancreas, intestines, lungs and ears. As a result, patients with FIC1 deficiency may have watery diarrhea, which can be severe, especially after liver transplantation. Patients with FIC1 deficiency can also have hearing problems, a chronic cough, and inflammation of the pancreas causing abdominal pain. Patients with BSEP deficiency may be at an increased risk of liver cancer. The liver disease in patients with severe FIC1 deficiency progresses more slowly than those with severe BSEP deficiency. However, there is still a great deal that



we do not yet know about the differences between FIC1 and BSEP deficiency and this will become clear as more patients are studied.

The milder form of FIC1 and BSEP deficiency are referred to as BRIC. BRIC is characterized by intermittent episodes of itching and jaundice. Between episodes, the liver disease appears to go away and there is no progressive injury to the liver itself. It is not clear what leads to the episodic cholestasis in individuals with BRIC. Some of these episodes may last for months. In some circumstances, the disease initially acts like BRIC, but over time it can become more persistent and has characteristics of PFIC.

The form of PFIC disease found in some patients with high serum GGT has been called PFIC-3, and is also called MDR3 deficiency. Patients with the severe form of MDR3 deficiency have very bad cholestasis in the first year of life, which may progress in the first few years of life toward cirrhosis and failure of the liver to perform its normal functions. However, there are less severe forms of MDR3 deficiency that cause milder disease, some of which are very responsive to medications. In these forms of MDR3 deficiency, the child and family may first become aware that there is something wrong during school age or adolescence. Sometimes, problems may not appear until adulthood or during pregnancy. The full spectrum of liver problems caused by MDR3 deficiency is just now becoming known.

How do you get PFIC?

PFIC is passed from parents to children (inherited) through genes. Genes are our genetic material, and are found within the chromosomes in the cells of our bodies. Genes are codes for each trait in our bodies. Each person receives two copies of each gene in their body: one copy from their mother and one from their father. For a child to get PFIC they must receive two changed copies of a gene, one each from the mother and the father. These changes in genes are called mutations. Carrying one changed copy of a gene and one normal copy of a gene does not usually cause disease, is called a carrier state and is relatively common. Thus parents of children with PFIC usually have no liver disease or the other potential manifestations of the disease. One exception to this may be that women with one changed PFIC gene may develop liver disease during pregnancy; in these women, the liver disease usually clears up after delivery.

What happens to the liver in PFIC?

The liver is one of the largest organs in the body and is found in the upper right part of the abdomen. It is very important to health because it cleans the blood and helps fight infections. The liver stores vitamins, sugars, fats and other nutrients and makes many substances that travel to the rest of the body. Another function of the liver is to break 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 presence of bilirubin in the skin and the whites of the eyes causes the yellow coloring known as jaundice. The term “liver disease” refers to a number of conditions that stop the liver from working as well as it should.

The liver cell (or hepatocyte) is responsible for making bile. Bile is a yellow fluid that the liver puts into the intestine by way of a system of tubes from liver to intestines, the bile ducts. Bile is a complex fluid that contains salts and waste products from the body. It also contains two main substances that are made from the body’s fats (lipids). These two substances, bile salts and phospholipids, act like detergents in bile and in the intestine. They help to dissolve fat and help vitamins to be absorbed from the diet. If the bile does not contain enough of these substances, this can cause stones to form in the bile ducts or injury to the cells lining the bile ducts. The changed genes in PFIC interrupt the way the liver cell normally puts bile salts (in FIC1 and BSEP deficiency) or phospholipids (MDR3 deficiency) into bile. This causes poor bile flow and a build-up of bile substances in the liver that is known as cholestasis.

The build-up of bile in PFIC causes the liver to be damaged. This eventually leads to scarring in the liver, which causes the liver not to work. This scarring eventually leads to cirrhosis, which can lead to other problems including accumulation of fluid in the abdomen (ascites) and bleeding from blood vessels in the esophagus, stomach or intestine (varices). Patients may also develop liver cancer.

How is PFIC diagnosed?

The patient is first examined by a physician familiar with childhood liver diseases. A thorough medical and family history is taken and a complete physical examination is performed. Ultrasound, CT scan or MRI testing of the liver may be done by a radiologist. Laboratory testing of blood, urine and tissues are the usual tests needed to find out the causes of these diseases. Often a procedure called a liver biopsy is performed to obtain a sample of liver tissue is taken for a pathologist to analyze.

The first tests are used to confirm that cholestasis is present. These include measuring bilirubin (the yellow pigment in bile), bile salts and liver enzymes, including GGT, in blood. Because, certain other pediatric liver diseases can look like PFIC, these diseases are tested. A liver biopsy is usually needed to help make the diagnosis and to find out if scarring is present. FIC1 and BSEP deficiencies are suspected when there is chronic cholestasis and low GGT. MDR3 deficiency is suspected when there is chronic cholestasis and high GGT. Special tests on the liver biopsies may help with the diagnosis. Genetic tests for these forms of liver disease are also available. These genetic tests are expensive and may not be covered by insurance.

What are the current therapies for PFIC and how well do they work?

Without any treatment, PFIC will lead to cirrhosis by age 10-20 years, and frequently earlier. Some mild forms may get better with ursodeoxycholic acid (a helpful bile acid) treatment. Severe disease does not usually get better with medical therapy. Young



children with PFIC may need to receive special infant formulas that contain MCT (medium chain triglycerides), a form of fat that is better absorbed in cholestasis. Other supplements that contain MCT may also be used in older children. Fat-soluble vitamin (A, E, D and K) monitoring and supplementation are also important. Children with BSEP deficiency, especially those with severe disease, should undergo regular screening (blood test and liver ultrasound) for liver cancer. A surgical procedure that removes bile acids from the body has been shown to help with relief of pruritus in the majority of patients. The most commonly used surgery is called a partial external/cutaneous biliary diversion. This means bile from the gallbladder is diverted to a bag that is kept on the surface of the skin of the abdomen. The bile is thrown away. Another surgery that has been tried is the limited ileal exclusion, in which there is a surgical bypass of the last 15% of the small intestine. This results in a diversion of bile salts to the colon where they are not absorbed. In many circumstances these two types of surgery can lead to a marked improvement in the pruritus and may slow the progression of the liver disease. A variation on these procedures, called nasobiliary drainage, has been tried in some adults with BRIC. In this procedure, a tube is placed in the nose and goes down to the bile ducts to drain bile. The pruritus diminishes dramatically after this procedure in adults with BRIC.

If liver failure develops, if a patient does not get better with surgical interventions, or if there is evidence of liver cancer, then liver transplantation may be needed. Liver transplantation involves removing a diseased liver and replacing it with a healthy one from another person. Survival after transplantation is excellent (>80-90%), although some medical problems may occur, some of which are specifically related to the form of PFIC. In FIC1 deficiency, these problems can include diarrhea, soreness of the pancreas, and build-up of fat in the liver. In BSEP deficiency, there may be recurrence of a disease similar to the original BSEP deficiency after liver transplantation. Even in the best circumstances, liver transplantation is not a complete cure; that is, the child who has had a liver transplant is not entirely healthy or entirely normal. Specific medical problems can occur after liver transplantation including the possibility of rejection and infection. In spite of these potential problems, liver transplantation permits survival and, as a rule, problems for the child and family after liver transplantation are easier to live with than problems for the child and family before liver transplantation.