PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC)

What is Progressive Familial Intrahepatic Cholestasis (PFIC)?

The name PFIC was coined in the early 1980s to describe a form of liver disease that was originally thought to primarily affect children, although it is now clear these disorders also impact adults. 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. “Byler’s disease” was used for Amish children with PFIC, in whom “PFIC” was first described in the 1960s. Early on three types of PFIC were identified and labeled as PFIC-1, PFIC-2, and PFIC-3, although since we now understand these conditions at a genetic level, these numeric terms are being used less and less. With advances in both understanding of the fundamental mechanism by which bile is formed and genetic investigations of individuals with cholestasis, the number of genes/proteins that are implicated in PFIC has grown (see Table below). The initial 7 of these genes/proteins are noted below.

Features of PFIC associated with different genetic defects			
Abnormal Protein	Mutated Gene	Affected areas	Additional information
FIC1	ATP8B1	Liver, lung, intestine, pancreas, hearing	• Historical PFIC1 • Intestinal disease (diarrhea) can worsen after transplant. • Possible fatty liver disease after transplant
BSEP	ABCB11	Liver	• Historical PFIC2 • Can recur after liver transplant
MDR3	ABCB4	Liver	• Historical PFIC3 • High GGT
TJP2	TJP2	Liver, lung, brain	

FXR	NR1H4	Liver	
MYO5B	MYO5B	Liver, intestine	• Isolated intestinal disease associated with microvillus inclusion disease
USP53	USP53	Liver, intestine, heart	

There are now many more genes that have been associated with bile flow problems in children. Bile flow problems are common in many severe liver diseases. As a result, a clear definition of what constitutes “PFIC” has become difficult.

Mutations in the genes lead to a failure to make normal versions of these proteins, which are important for the formation of bile, 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. There are 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 at all often, although not always, result in more 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.

What are the symptoms of PFIC?

A hallmark of PFIC is the development of cholestasis (poor bile flow), which can be variably associated with certain symptoms and problems including, pruritus (the feeling of being itchy), jaundice (yellow skin or eyes), nutritional deficiencies (including poor growth and fat-soluble vitamin [A, D, E and K] deficiencies) and eventually potential complications of progressive liver disease/cirrhosis. Some of the proteins encoded by these genes are found outside the liver and as such symptoms and problems that are not liver based can develop (e.g., hearing loss in FIC1 disease)

Most of these diseases cause cholestasis that begins in early childhood, with the average age at onset of symptoms being infancy. 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 standard medications for itching. The scratching interferes with normal activities and sleep and may therefore hinder learning and schoolwork.

Problems with growth are another potential 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 stones in their gallbladder or bile ducts. Many patients have an enlarged liver or enlarged spleen.

There are somewhat unique problems that can be seen with each of the different gene defects that lead to PFIC (problems that can occur after liver transplant are described below).

FIC1 disease often becomes apparent during infancy and can be associated with problems outside the liver including hearing loss, inflammation of the pancreas (pancreatitis), or diarrhea.

Patients with BSEP disease also develop signs of liver disease during infancy, and they may be at a significantly increased risk of liver cancer.

MDR3 related disease causes progressive liver disease like FIC1 and BSEP disease do, but it often may not become apparent until later in childhood. It may also be associated with the development of stones in the bile ducts and the gallbladder. Cancer of the bile ducts is a rare problem for adults. Of the seven PFIC disorders in the list above, this is the only one associated with an abnormally high serum (blood) gamma-glutamyltransferase (GGT – aka GGTP) level. MDR3 disease is associated with a predisposition to developing stones in the gallbladder and bile ducts. A unique issue in

MDR3 disease is the development of stones or sludge in the bile ducts within the liver. This latter problem is known by the abbreviation LPAC.

TJP2 disease, like BSEP disease, may be associated with liver cancer. Problems outside the liver may include hearing impairment. TJP2 disease was discovered much later than BSEP disease and therefore we may still discover new things about it including problems outside the liver.

FXR disease typically appears during infancy and progresses rapidly, often to liver failure. FXR is important for the production of clotting factors, so bleeding may be a more prominent issue in FXR disease. This may be distinct from the bleeding problems related to vitamin K deficiency. FXR also drives the production of BSEP, so FXR disease has many similarities to BSEP disease. Problems outside of the liver have not yet been reported, but FXR is found outside the liver so issues may be identified with further follow up of individuals with FXR disease.

MYO5B liver disease commonly appears during infancy or the toddler years as isolated liver disease, and severe itching is particularly common in this disorder. Mutations in the MYO5B gene also cause microvillus inclusion disease (MVID), a severe diarrheal disease that sometimes necessitates intestinal transplant and was discovered much earlier than MYO5B liver disease. MYO5B liver disease may occur alone, along with MVID, or it may develop after intestinal transplant for MVID.

USP53 liver disease appears to be milder than most of the other PFIC disorders, based on what we know about this recently discovered disease. It may go away on its own or with treatment with a medication called rifampin. Gallstones have been reported, and, outside the liver, hearing loss has been reported in some children with USP53 liver disease.

Milder forms of PFIC 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 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 or progressive, which is characteristic of PFIC.

Another form of disease that can occur due to mutations in the PFIC genes is intrahepatic cholestasis of pregnancy (ICP), which can cause itching and/or jaundice during pregnancy and may necessitate an early delivery of the baby to avoid other potential complications for the mother or baby.

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. MDR3 disease is an exception to this process and individuals with one copy of the gene that is mutated can develop disease. In addition, women with one changed PFIC gene may develop liver disease during pregnancy; in these women, the liver disease usually resolves 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, helps the blood to properly clot, and helps fight infections. The liver 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 can cause abnormal blood test results, jaundice, scarring in the liver, or 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 secretes components of 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 can eventually lead to cirrhosis. Cirrhosis 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). Cirrhosis and on-going liver injury can make the liver not work right, sometimes called end-stage liver disease. Patients may also develop liver cancer.

How is PFIC diagnosed?

In order to make a diagnosis of PFIC, the patient is examined by a physician familiar with childhood liver diseases. A thorough medical and family history is taken, and a complete physical examination is performed. A radiologist may do tests to look at the liver. Laboratory testing of blood and urine can help determine the type of liver disease and severity of that disease. Genetic testing is often done to make a specific determination of the type of PFIC. These tests are not always definitive and other tests may be required to understand the liver disease including a liver biopsy.

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

Without any treatment, many of the forms of PFIC may lead to cirrhosis during childhood, adolescence or early adulthood. Some forms of PFIC get better with medications that block intestinal absorption of the bile acids made by the liver. This type of medication, called intestinal bile acid transporter inhibitors (iBAT inhibitors), often reduces itching and improves sleep hygiene. Sometimes doctors recommend ursodeoxycholic acid (a “good” bile acid) to support liver. This treatment may be most effective for milder forms of MDR3 disease. Severe types of PFIC often do not 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 and TJP2 disease, especially those with severe disease, should undergo regular screening (e.g., blood test and liver ultrasound) for potential liver cancer.

While surgical procedures have been shown to help with the relief of pruritus (itching) in many patients with PFIC, recent advancements in medical treatment are providing new options. Traditionally, the most commonly used surgery has been a partial external/cutaneous biliary diversion. This procedure diverts bile from the gallbladder to a bag that is kept on the surface of the skin of the abdomen, with the bile being discarded. Another surgical option is ileal exclusion, which involves a surgical bypass of the last 15% of the small intestine, diverting bile salts to the colon where they are not absorbed. These types of surgery can often lead to a marked improvement in itching and may slow the progression of liver disease. However, recent clinical studies have shown that iBAT inhibitors may achieve similar outcomes to these surgeries – in particular the impact on pruritus/itching. As iBAT inhibitors are non-invasive, a major advantage of their use relates to avoiding complications of surgery and the poor acceptance of an ostomy required for biliary diversion. These medications are increasingly becoming the first choice for managing PFIC, reducing the need for surgical interventions. These are new medications and long-term follow-up will be needed to assess their impact on the progression of disease in PFIC.

If a patient develops severe complications of liver scarring, if their liver fails or if there is a concern for or diagnosis of liver cancer, a liver transplant is indicated. This means their sick liver is replaced with a healthy one from someone else. People usually do well after a transplant, with over 80-90% of them surviving. Liver transplantation is however potentially associated with a finite risk of death in the first years after the procedure, and also complications of the surgery and the medications necessary to prevent rejection of the transplanted liver.

In some circumstances, liver transplant does not fully address the underlying problem of PFIC. Patients with FIC1 deficiency can have serious diarrhea, pancreas damage, and fat buildup in the liver after transplant. It is not known whether biliary diversion of IBAT inhibitor therapy may help with these issues. Patients with BSEP deficiency can have jaundice and itchiness, similar to what they experienced before the transplant. This is the result of an immune reaction against the BSEP protein in the new liver – this problem acts like a "recurrence" of the original BSEP disease. There are limited reports of fatty liver disease after transplant for FXR disease.

Does ChiLDReN have any studies that include patients with PFIC?

Yes. ChiLDReN currently has one study that includes patients with PFIC.

The LOGIC study is a natural history study that includes patients with PFIC and three other rare liver diseases. A natural history study is aimed at acquiring information and data that will provide a better understanding of rare conditions. Participants will be asked to allow study personnel to obtain information from medical records and an interview, and to collect blood, urine, and tissue samples when clinically indicated, in order to understand the causes of these diseases and to improve the diagnosis and treatment of children with these diseases. All of the information obtained in these studies is confidential and no names or identifying information are used in the study.

LOGIC: A longitudinal study of genetic causes of intrahepatic cholestasis.

Eligibility: Children and adults ages 6 months through 25 years diagnosed with Alagille Syndrome, alpha-1 antitrypsin deficiency, progressive familial intrahepatic cholestasis, or bile acid synthesis defects, both before and after liver transplantation.

ClinicalTrials.gov Study NCT00571272

Are there any organizations or foundations that help families dealing with PFIC?

Yes. The ChiLDReN Network works with numerous groups that support patients and families who are dealing with rare liver diseases. Please click here to go to that page on our website (Information for Families). You will see the list of groups and information about them. https://childrennetwork.org/families.aspx