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Homozygous Familial Hypercholesterolemia

What is Homozygous Familial Hypercholesterolemia?

Homozygous Familial Hypercholesterolemia, or HoFH, is a rare genetic condition where people have very, very high levels of a type of cholesterol in their blood called low-density lipoprotein cholesterol (LDL-C). People who have this condition are at very high risk of early heart disease (heart attack or stroke)

if their high cholesterol is not treated. FH is caused by changes in a gene that lowers the body's ability to remove the LDL-C from the blood, which makes the levels of LDL-C in the blood very high. Cholesterol builds up in the walls of arteries forming hard structures called plaques. Over time, these plaques can block the arteries and cause heart attacks or strokes.

Most people with Familial Hypercholesterolemia have the more common form, heterozygous familial hypercholesterolemia, sometimes shortened to HeFH or to FH. However, if you or your child have an LDL-C > 400mg/dL, a diagnosis of HoFH should be considered.

FH is usually passed from parent to child, and in most cases, both parents of a child with HoFH have the more common form of FH. If a person is diagnosed with either type of FH, their parents, siblings, and children should all have their cholesterol checked.

HoFH is a rare disease. Worldwide, about 1 in 150,000 to 1 in 400,000 people have HoFH.

Criteria for Diagnosis of HoFH in Children and Adolescents:

HoFH can be diagnosed by measuring blood cholesterol levels and asking about heart disease in relatives, or it can be diagnosed through genetic testing.

While there are some differences in guidelines, the following criteria can be used to diagnose FH in children, adolescents, and young adults (less than 20 years old):

1. The person has LDL-C ≥ 400 mg/dL after other causes of high LDL-C have been looked for, and one or both parents have clinically diagnosed FH (link to pediatric and adult FH pages).

2. Genetic testing shows the person has a pathogenic or likely pathogenic mutation in two copies of a gene associated with FH. They can have two copies of the exact same mutation, or they can have a different mutation in the same or different genes.

Genetic testing for people with suspected HoFH is very strongly recommended because it will help decide which medications will be the most effective for treatment.

What Does a Diagnosis of HoFH Mean for My Child?

Children with HoFH have very high blood levels of LDL-C that will significantly raise their risk for a heart attack or a stroke if they are not properly treated. These heart attacks and strokes can happen in children as young as 4 years old, so early diagnosis and treatment are very important. They also are at

high risk of developing narrowing in their aortic valve (called aortic stenosis) and can have bumps on their skin called xanthomas that are due to cholesterol build up under the skin's surface.

For many people, high cholesterol can be the result of a lifestyle that includes a diet high in saturated or trans-fat, not getting enough exercise, having an unhealthy weight, or having another medical condition like a low thyroid level or diabetes. However, children with FH can be a healthy weight, have a healthy diet, get plenty of exercise, and still have high LDL-C.

For all people with FH, a healthy lifestyle is very important but people with HoFH will require medications, usually more than one medication, to help lower their LDL-C level. Sometimes other types of treatment are needed to help reduce LDL-C levels in the blood. All people with HoFH should be in the care of a lipid specialist. They usually need monitoring tests including echocardiograms, CT scans, and sometimes cardiac catheterizations.

Treatment Options for Children with HoFH:

Guidelines recommend that children with a diagnosis of HoFH start taking medication to lower their LDL-C starting as soon as they are diagnosed. The first choice in most cases is a type of medication called a statin but usually more than one medication is needed. Listed below are some of the medication options to treat pediatric FH:

Statins: Statins are medications that lower cholesterol and have been widely used across the world for many years. Examples of statins include simvastatin, rosuvastatin, atorvastatin, pitavastatin, and pravastatin. By preventing the storage and production of cholesterol in the liver, statins reduce the number of cholesterol particles in the blood that can otherwise build up and lead to heart attacks and strokes. All statins are FDA approved for use in children, some as young as 8 years old, others at age 10 and older. Statins are pills that are taken by mouth, once daily, either with or without food. Statins can usually be taken with other medications. Some people can experience muscle aches with statins; however, they are usually well tolerated, and muscle aches are very rare in children. If this occurs, please talk to your Healthcare Team to decide if any new aches are related to the statin medications or related to activities like playing or exercising. Among patients without HoFH, these medications have been found to lower LDL-C by about 20% to more than 50% depending on the dose; however, patients with HoFH may have variable responses based upon their specific gene mutation.

Ezetimibe: Ezetimibe may be used in addition to a statin or on its own based on the individual child's needs and tolerance to other medications. Ezetimibe is a commonly prescribed medication that is well-tolerated. Ezetimibe works by modifying how much cholesterol is absorbed from food in the gut to the bloodstream. Ezetimibe is FDA-approved for use in children 10 years of age or older. Ezetimibe is a pill that can be taken once daily, with or without food. Ezetimibe has few side effects but may include abdominal pain, flatulence, or diarrhea. These medications have been found to lower LDL-C by an additional 20% beyond statin therapy.

PCSK9 inhibitors: PCSK-9 inhibitors are medications typically used in addition to statin therapy but may be used on their own based on the child's needs. One of the PCSK-9 inhibitors, evolocumab, is approved by the FDA for use in children 10 years or older. These medications are an injection that can be administered into an area of fat tissue, such as the abdomen, at home by a family member and given to

a child every 2 weeks or every 4 weeks depending on the dose prescribed by the Healthcare Team. PCSK-9 inhibitors are generally well tolerated but can cause irritation, redness, or itchiness when injected. These medications have been found to lower LDL-C by about 45% to 60% beyond statin therapy.

Evinacumab: Evinacumab is used specifically in children with HoFH who are 5 years of age and older in addition to other cholesterol-lowering therapies to lower LDL-C. Patients prescribed evinacumab may also be undergoing lipid apheresis (see below). Evanicumab works in the body by helping to increase the activity of molecules that break down cholesterol. This medication is dosed based upon a patient's body weight and administered by a healthcare professional through an intravenous (IV) infusion directly into the bloodstream every 4 weeks. This medication is generally well tolerated and side effects mainly consist of flu-like symptoms. These medications have been found to lower LDL-C by over 50% beyond other cholesterol-lowering therapies.

Inclisiran: Inclisiran is a part of a new class of medications used in addition to statin therapy to significantly decrease LDL-C. Although currently not specifically indicated for use in children, including adolescent patients, with HoFH, ongoing trials aim to demonstrate safety and efficacy in this population. Despite this, some providers may recommend the use of this medication if other therapies are not effective and benefits outweigh risks. Inclisiran works by modifying how effectively the liver removes LDL-C from the blood. This medication needs to be administered by a healthcare professional and is injected into an area of fat tissue; however, it is only administered every three to six months. Inclisiran is generally well tolerated with the most common side effects being redness or irritation at the injection site and less commonly, joint pain or cold-like symptoms. These medications have been found to lower LDL-C by more than 50% beyond statin therapy.

Bile acid sequestrants: Bile acid sequestrants are used less commonly; however, they may serve as a beneficial addition to a child's regimen to further lower cholesterol. Examples of these medications include cholestyramine and colesevelam. Bile acids are natural chemicals in the body that break down cholesterol from food in the gut to absorb cholesterol in the blood. Bile acid sequestrants are medications that bind with these substances in the gut to help prevent the absorption of cholesterol from food. This medication is commonly a powder that can be measured at the dose provided by your Healthcare Team and mixed into juice, water, or semi-solid food with a high liquid content, like applesauce. It is also available in pill form although the pills are large, and several are needed per dose. Given that these medications stay in the gut and block absorption to the bloodstream, it is advised that these medications be taken one hour before or four to six hours after other medications to ensure that the doses of other medications are properly absorbed. These medications are not absorbed and stay in the gut, which can lead to some side effects such as upset stomach, constipation, or heartburn. Typical LDL-C reduction is about 20%. The effect is additive with statins.

For all of these medications, it is important to talk to your Healthcare Team prior to starting any new medications or supplements to ensure that they are safe to take with the prescribed medications. Following the start of new medications, dose adjustments, or discontinuation of certain cholesterol-lowering medications, your Healthcare Team will request repeat laboratory tests to check the impact of the medication on cholesterol levels, which can serve as a marker for risk of heart disease. Additional monitoring tests, such as liver tests, may be needed on a less frequent basis. As always, if you have any concerns with medications, please discuss them with members of your Healthcare Team.

Lipid Apheresis: LDL apheresis is a medical therapy for patients who are not able to meet their LDL cholesterol goal with medicines and lifestyle changes. This procedure physically removes LDL cholesterol from the blood. Blood is removed from one arm and goes through a special filtering machine that removes LDL cholesterol. The newly filtered blood, with a much lower LDL level, is then returned to the other arm. Medical professionals monitor patients during the procedure, which takes 2 to 3 hours and is generally performed once every other week.

Liver transplant or heart/liver transplant: LDL-C is removed from the blood by the liver. Liver transplantation can be done to help restore the ability to clear LDL-C in children with HoFH. If a person with HoFH also has abnormal heart function due to plaque buildup and/or previous heart attacks, a heart transplant is sometimes performed at the same time as a liver transplant. This treatment is not used very often and is only done in specialized medical centers.

Lifestyle Recommendations for Children with HoFH:

Lifestyle recommendations for children with HoFH are very similar to lifestyle recommendations for all people. Eating a wide variety of foods with plenty of fruits and vegetables, lean proteins (chicken, turkey, tofu, and fish are a few examples), and whole grains are key to keeping LDL-C levels as low as possible. Reducing the amount of saturated fat, cholesterol, and trans-fat in the diet can also help lower LDL-C.

Regular physical activity is also very important! Encourage your child to try different activities to find something they like. Ideally, they will want to continue an active lifestyle on their own.

Finding a Pediatric FH Specialist in Your Area:

Pediatric lipidology, or the treatment of high cholesterol in children, is a small but growing field in medicine. Some pediatric HoFH specialists are pediatric cardiologists, some are pediatric endocrinologists, some are pediatricians, and some are adult lipidologists with an interest in caring for children with high cholesterol.

It can be challenging to find a pediatric HoFH specialist. Your child's primary care provider may know the pediatric lipid specialists in your area. On the website for your health care system, review providers in pediatric cardiology and pediatric endocrinology and look for key interests like "lipid clinic", "cholesterol", or "preventive cardiology", or search those terms under medical conditions the system treats. We recommend that if you are interested in additional patient educational materials, you visit The Family Heart Foundation at www.familyheart.org, or to find a provider in your area you can use our Find a Clinician Tool.