CONDITION

Homozygous familial hypercholesterolemia

Homozygous familial hypercholesterolemia is an inherited condition that causes extremely high LDL cholesterol from birth.

WHAT IT IS
Severe inherited lifelong elevation of LDL cholesterol

BODY SYSTEM
Heart and circulation

MAIN SYMPTOMS
Cholesterol deposits, corneal rings, chest pain, breathlessness

WHAT CAUSES IT
Inherited changes affecting cholesterol removal

HOW IT IS DIAGNOSED
Repeated cholesterol tests, family assessment, genetic testing

MAIN TREATMENT
Specialist cholesterol medicines and LDL apheresis

CAN IT BE CURED?
No - inherited cholesterol changes remain lifelong

IS IT AN EMERGENCY?
Sometimes - chest pain or stroke signs

LONG-TERM OUTLOOK
Early treatment lowers but does not remove heart risk

Overview

Homozygous familial hypercholesterolemia, often shortened to HoFH, is a rare inherited condition. It causes very high levels of low-density lipoprotein cholesterol, or LDL cholesterol, from birth.

LDL carries cholesterol through the blood. It is sometimes called "bad cholesterol" because high levels can lead to fatty deposits inside arteries. In HoFH, the body cannot remove LDL from the blood normally.

"Homozygous" usually means that a person inherited a gene change affecting LDL clearance from both parents. The exact genetics can be more complex, and different genes may be involved.

Without effective treatment, cholesterol can build up in arteries during childhood. This can cause coronary artery disease, which reduces blood flow to the heart, much earlier than in the general population. Cholesterol may also damage the aortic valve and the first part of the aorta, the body's main artery.

HoFH needs lifelong care from a specialist lipid service. Treatment started early can substantially lower LDL cholesterol and reduce the risk of complications, although reaching usual cholesterol targets can be difficult.

Symptoms

High LDL cholesterol itself does not usually make you feel unwell. Some people are diagnosed through family testing or a cholesterol blood test before they develop symptoms.

Visible cholesterol deposits can provide an early clue. These may appear in childhood and include:

These deposits are called xanthomas. They are not usually dangerous themselves, but they can indicate prolonged exposure to very high cholesterol. Similar changes can occur for other reasons, so their appearance alone does not confirm HoFH.

If arteries or the aortic valve have become narrowed, symptoms may include chest pressure, shortness of breath, tiredness with activity, dizziness or fainting. Symptoms may first appear during exercise because the heart needs more oxygen at that time.

Children may adjust their activity without describing symptoms clearly. A child who regularly stops during play, avoids exercise or reports chest discomfort needs medical assessment.

- Firm yellowish lumps over tendons, especially the Achilles tendons or hands
- Flat or raised yellow areas around the elbows, knees, buttocks or between the fingers
- Yellow patches around the eyelids
- A pale or white ring around the edge of the cornea, the clear front surface of the eye

Causes and risk factors

HoFH is caused by inherited gene changes that interfere with the removal of LDL cholesterol from the blood. The most commonly involved gene is LDLR , which provides instructions for making the LDL receptor. This receptor helps liver cells take LDL out of the bloodstream.

Other forms can involve genes such as APOB , PCSK9 or LDLRAP1 . These genes affect how

the LDL receptor binds to LDL, how long receptors remain active or how they work inside cells.

The amount of working LDL-receptor activity differs between people. This helps explain why LDL levels, treatment response and the age at which complications appear are not identical for everyone with HoFH.

HoFH is inherited. It is not caused by eating habits, body weight or lack of exercise. Food choices can affect cholesterol levels and overall heart health, but lifestyle alone cannot explain or control the severe LDL elevation caused by this condition.

Parents and siblings may also have familial hypercholesterolemia. When both parents have a single disease-causing change in the same relevant gene, each pregnancy may have a chance of resulting in HoFH. The pattern can differ when other genes or more than two gene changes are involved. Genetic counselling can explain the inheritance pattern for a particular family.

Diagnosis

Diagnosis begins with a lipid profile, a blood test that measures LDL and other blood fats. In HoFH, untreated LDL cholesterol is usually extremely high. Results are interpreted alongside age, previous treatment, family history and physical findings.

The clinician will ask about high cholesterol and early heart disease in parents, siblings and other close relatives. They may look for tendon or skin xanthomas and examine the eyes for a corneal ring.

Genetic testing can identify changes in genes linked to familial hypercholesterolemia and may confirm the diagnosis. It can also help guide family testing. However, testing does not find every possible genetic cause. A negative result does not automatically rule out HoFH when the cholesterol pattern and family history strongly support it.

Other blood tests may be used to look for conditions that can raise cholesterol, such as an underactive thyroid, kidney problems or certain liver conditions.

Because artery and valve changes can develop early, assessment may include an electrocardiogram, heart ultrasound or imaging of the coronary arteries and aorta. The choice and timing of tests are based on age, symptoms, previous results and local specialist practice.

Close relatives are usually offered cholesterol testing and, when a familial gene change is known, targeted genetic testing. This process is called cascade testing.

Treatment and management

Treatment aims to lower LDL as much and as early as safely possible. It also aims to detect and manage artery or valve problems before they cause lasting harm.

Most people need several treatments because one approach is rarely enough. Care is usually coordinated by a lipid specialist, with input from cardiology, paediatrics, genetics and specialist nursing when needed.

Statins like atorvastatin or simvastatin reduce the liver's production of cholesterol and increase LDL removal. Ezetimibe reduces cholesterol absorption from the intestine. These are commonly used as part of combined treatment, although their effect may be limited when very little LDL-receptor function remains.

Other medicines may be considered. PCSK9 inhibitors help preserve LDL receptors and work best when there is some remaining receptor activity. Evinacumab blocks ANGPTL3, a protein involved in fat metabolism, and can lower LDL without relying mainly on the LDL receptor. Lomitapide reduces the production of lipoproteins that later form LDL.

Availability and approval for these treatments differ by country, age and individual circumstances. Some require injections, monitoring or careful management of side effects. Pregnancy or plans for pregnancy can change which treatments are appropriate, so early discussion with the specialist team is important.

LDL apheresis may be needed. This is a procedure in which blood passes through a machine that removes LDL before the blood returns to the body. It must be repeated regularly because LDL rises again between sessions. Access to apheresis and the schedule used differ between treatment centres.

Liver transplantation may greatly improve LDL clearance because the new liver provides functioning LDL receptors. It is considered only in selected situations because transplantation carries major surgical risks and requires lifelong medicines to prevent rejection.

Eating patterns that limit saturated fat and support heart health can complement medical treatment. Regular activity, avoiding smoking, managing blood pressure and caring for diabetes also reduce overall cardiovascular risk. These measures are valuable, but they do not replace specialist LDL-lowering treatment.

Complications

The main complication is atherosclerosis, the buildup of cholesterol-rich plaque inside arteries. In HoFH, this process can begin in childhood.

Narrowing of the coronary arteries can cause angina, a heart attack or reduced heart function. Cholesterol can also collect around the aortic root and valve, leading to narrowing called aortic

stenosis. This may cause breathlessness, chest discomfort, dizziness or fainting.

Arteries carrying blood to the brain or limbs can also be affected, although coronary and aortic disease are especially important in HoFH.

The chance and timing of complications are influenced by lifelong LDL exposure, the amount of remaining LDL-receptor function, treatment response and other risks such as smoking, high blood pressure or diabetes. A lack of symptoms does not mean that arteries are unaffected, which is why planned monitoring remains important.

Prevention

HoFH itself cannot currently be prevented because it is inherited. Nothing a parent did during pregnancy causes the condition.

Complications may be delayed or reduced through early diagnosis, sustained LDL lowering and regular assessment of the heart, arteries and aortic valve. Taking treatment consistently matters because LDL rises when many treatments are stopped or delayed.

Family testing can identify children and adults who have inherited familial hypercholesterolemia before symptoms develop. Genetic counselling can explain reproductive options without directing personal decisions.

Living with it and what to expect

HoFH is lifelong. LDL cholesterol remains high without ongoing treatment, even when you eat well, exercise and feel healthy.

Treatment often becomes part of the weekly or monthly routine. This may involve tablets, injections, blood tests, clinic visits or apheresis sessions. Children and teenagers may need support around school attendance, procedures and taking increasing responsibility for their care.

The treatment plan may change over time as new medicines become available, LDL response becomes clearer or heart imaging shows a need for closer monitoring. Visible xanthomas may shrink when LDL is lowered, but this is not a reliable measure of what is happening inside the arteries.

Many people continue with education, work, relationships, travel and physical activity. Exercise advice may need to be adjusted if coronary artery or aortic valve narrowing is present. A cardiology team can advise on safe activity based on test results rather than the diagnosis

alone.

The outlook has improved as diagnosis has become earlier and more treatment options have become available. Even with treatment, cardiovascular risk remains higher than average, so lifelong specialist follow-up is needed.

When to get medical help

Arrange routine contact with your specialist team if treatment is causing side effects, appointments or apheresis sessions have been missed, or you are having difficulty following the plan. New exercise intolerance, occasional chest discomfort, breathlessness, dizziness or unexplained tiredness also needs prompt assessment rather than waiting for the next routine review.

Contact the care team early if you are pregnant, think you may be pregnant or are planning a pregnancy. Do not stop prescribed treatment without medical advice unless emergency instructions say otherwise.

Seek emergency help for:

These symptoms can have several causes, but they require urgent assessment.

- Chest pressure or pain that is severe, persistent or occurs at rest
- Chest discomfort with sweating, nausea, breathlessness or pain spreading to the arm, jaw or back
- Sudden weakness, facial drooping, speech difficulty or loss of vision
- Fainting, especially during activity or with chest symptoms
- Sudden severe breathlessness

Common questions

Is homozygous familial hypercholesterolemia the same as ordinary high cholesterol?

No. HoFH causes extreme LDL elevation from birth because of inherited changes in cholesterol clearance. Ordinary high cholesterol often develops through a mixture of genes, age, health conditions and lifestyle factors.

Can I have HoFH without any symptoms?

Yes. High LDL usually causes no immediate sensation. Artery changes can develop before chest pain or breathlessness appears, so regular testing and imaging may be needed even

when you feel well.

Will changing my diet bring my LDL down to normal?

Diet can support heart health and may lower LDL to some extent, but it cannot correct the inherited problem that causes HoFH. Most people need several specialist treatments.

What is the difference between HoFH and heterozygous familial hypercholesterolemia?

Heterozygous familial hypercholesterolemia usually results from one inherited gene change and generally causes less severe LDL elevation. HoFH usually involves two disease-causing changes and tends to cause earlier cardiovascular problems.

Can my children inherit it?

Yes. The chance depends on your genetic result and whether the other biological parent has a familial hypercholesterolemia gene change. Genetic counselling and testing can clarify the likely inheritance pattern.

Does LDL apheresis permanently remove the cholesterol?

No. Apheresis lowers LDL at the time of treatment, but the body continues producing cholesterol-containing particles. LDL therefore rises again, and the procedure usually needs to be repeated.

Sources

- European Atherosclerosis Society Consensus Panel. "2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: New Treatments and Clinical Guidance." European Heart Journal , 2023
- National Center for Biotechnology Information. "Familial Hypercholesterolemia." GeneReviews , NCBI Bookshelf
- National Institute for Health and Care Excellence. Familial Hypercholesterolaemia: Identification and Management . Clinical guideline CG71
- US Food and Drug Administration. EVKEEZA (evinacumab-dgnb) Prescribing Information
- US Food and Drug Administration. JUXTAPID (lomitapide) Prescribing Information
- Cuchel M, Bruckert E, Ginsberg HN, and colleagues. "Homozygous Familial Hypercholesterolaemia: New Insights and Guidance for Clinicians to Improve Detection and Clinical Management." European Heart Journal , 2014