Because familial hypercholesterolemia predisposes affected individuals to heart attack and stroke, identifying and treating this silent killer are critical.

Familial Hypercholes

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A Silent and Symptomless Killer

By **JULIANN SCHAEFFER**

Familial hypercholesterolemia (FH), a genetic cause of high cholesterol, is by no means a rare disorder, but it is rarely diagnosed, making a silent killer of this often-symptomless genetic mutation that can cause heart attacks in young, fit, non-smoking patients.

Although a typical patient presenting with high cholesterol—very high, in fact—may be older with a history of smoking and may enjoy a high-fat or high-cholesterol diet, none of these is a prerequisite for FH patients, which makes diagnosis and early treatment particularly critical.

Alan Brown, MD, a cardiologist who has run a cholesterol clinic for 29 years and is on the board of the National Lipid Association, explains: "I was once referred a 62-year-old woman who never smoked but had a history of very high cholesterol from her family doctor. She had a total cholesterol over 300 and LDL cholesterol was 220, so she fit with FH. The reason she was referred to me was not because her doctors had made this diagnosis, however, but it was because she couldn't find a cholesterol drug that she could tolerate.

"In the meantime, I asked her if she ever had her children tested because it's particularly dangerous in young men, and she said she had not," he continues. "I told her to make sure she alerted her two daughters, who were in their 30s, and her son, who was 28 and an Army Ranger. The two daughters were tested, and their blood looked normal. The son said that since he was in the Army, they would have notified him if his cholesterol was high, and he refused to get the test done. Three weeks later, he died suddenly during an Army Ranger exercise."

Stories like this are all too common, Brown says, partly because FH can cause fatal complications in young, healthy individuals and partly because many physicians simply are unaware of FH as a whole. "So the biggest thing is not just understanding what the disease is in terms of the mutation," he says. "The biggest thing is to make it clear to families that if their LDL cholesterol is over 190, their children have to be tested. Because with FH, boys get heart disease in their 20s or 30s, even if they don't smoke. Girls seem to do a little better, but if they smoke, half of them will have heart disease by the age of 35. It's important."

Characteristics

What specifically is FH? "It is a genetic disorder when someone inherits either one or two genes from their parents," says Robert C. Block, MD, MPH, an associate professor in the division of cardiology at New York's University of Rochester, noting that it's not caused by eating the wrong foods or by inadequate exercise. The genetic defect makes the body incapable of removing LDL cholesterol from the blood, resulting in much higher than normal levels of LDL in the blood.

As Brown explains, the body makes cholesterol in the liver and uses it for various purposes, such as making certain hormones and producing bile. For most people, LDL receptors on the liver's surface clear this cholesterol from the blood. "With FH, patients inherit from one parent a bad gene for their LDL receptors and from the other parent a good gene, so only half of their LDL receptors work, and therefore, the amount of LDL in their blood doubles because their body can only remove it at half the rate," he says.

This inhibited function predisposes affected individuals to premature heart attacks and strokes, Block says, noting that more patients with FH will suffer a heart attack than a stroke.

"For some reason, it primarily manifests as heart attack rather than stroke," says Paul N. Hopkins, MD, MSPH, codirector of the cardiovascular genetics division at the University of Utah and director of the Cardiovascular Disease Prevention Clinic who has done extensive research among patients with FH. "Whether that's because the people who are strongly predisposed to develop atherosclerosis when they have the high cholesterol develop heart attacks first and die before they get to a stroke, it's not really known. But certainly heart attacks are the obvious danger with FH."

"One girl [with FH] had her first heart attack at the age of 6," Block says. "Most patients will have their first heart attack in their 20s, 30s, or 40s unless they are treated effectively."

Heterozygous FH occurs when a patient inherits one bad gene. This disorder is common, affecting between one in 300 and one in 500 people in the United States. Homozygous FH, while more rare, is exponentially more dangerous and occurs when a patient inherits two bad genes for LDL receptors, resulting in having no LDL receptors that work properly.

It's estimated that one in 1 million people have homozygous FH, "and it's devastating," Brown says. "Cholesterol levels for these patients are well over 1,000, and kids with homozygous FH usually have heart disease by age 10 or 12."

Because it's a dominant trait, heterozygous FH patients have a 50/50 chance of passing along the gene and the disorder to their children, which is the reason Brown says it's critical that all first-order family members be screened when a patient is diagnosed with FH and the reason diagnosis is important in the first place. "The important thing is that it's fairly common," he says.

In fact, Hopkins says FH is more common than type 1 diabetes. "It needs to be recognized, first so that the patients themselves can be treated early and throughout their lives, and especially so their kids and family members can be identified and treated more effectively," thereby reducing coronary disease and heart attacks in affected individuals, he notes.

Because many physicians are unaware of this disorder, the majority of patients with FH are treated as simply having high and hard-to-manage cholesterol levels. Hopkins estimates that only 3% to 4% of FH patients are properly diagnosed. "Some say 1% of FH patients are properly diagnosed," he notes. "There are over 600,000 patients and most are not getting properly treated by current estimates."

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When FH individuals aren't properly diagnosed, not only is their cholesterol harder to manage, as FH patients typically need more than statins alone to sufficiently reduce their numbers, but an opportunity is missed for other family members to be diagnosed, particularly children. Especially because many people aren't screened for cholesterol until they're in their 30s or 40s, children with the disorder are left to deal with the consequences of years of untreated high cholesterol before it's identified, if it's identified at all.

Hopkins notes that several organizations are taking notice and trying to spread the word to prevent these circumstances. "The CDC [Centers for Disease Control and Prevention] has made a particular push to promote family screening to find FH patients," he says, adding that pediatric guidelines have been altered to promote general population cholesterol screening at a young age, primarily so that FH patients can be found and treated when they're children. "The pediatric guidelines now suggest starting statins as young as 8 and certainly by 12 for FH patients," he says. "There's a big recognition and a need to much more aggressively find and treat people with FH."

"There are a lot of efforts through the National Lipid Association and the FH Foundation to increase awareness among physicians about the disorder," Brown says. "It is the most common inherited metabolic disorder."

Diagnosis

How should physicians identify and diagnose the condition and distinguish FH from a patient who simply has high cholesterol due to lifestyle factors? According to Hopkins, it's a matter of magnitude. "The average cholesterol for someone in the US over 30 years old is about 130," he says. "Most people with FH have LDLs well over 190, so it's about double, at least, what the general population's level is. Looking at family lipid levels can also help confirm a diagnosis of FH. Usually, it's obvious who carries the gene and who doesn't."

Block agrees, noting that physicians should suspect FH in patients with an LDL cholesterol level greater than 190 and total cholesterol levels greater than 250. "They can also have other manifestations of very high levels of cholesterol, including thickened Achilles' tendons and tendons on the hands."

If FH is suspected, Brown says several tests should be performed to confirm that nothing else is responsible for the high cholesterol levels, such as an underactive thyroid. "It's mostly a patient's cholesterol levels and finding an immediate relative who has very high cholesterol or had an early heart attack," he says. "There's very few other things that will give you that high of a cholesterol."

Because patients' primary care physicians direct the management of high cholesterol, it's largely up to them to recognize FH manifestations and recommend that patients have their family members screened appropriately. "Raising awareness of the disorder is the biggest thing," Brown says. "Every doctor needs to know about this because it is so common. Most adults get a cholesterol test as part of their routine physical, but the average physician isn't aware of this disorder, and because of that, a lot of children and younger family members go undiagnosed for way too long. Or physicians don't treat aggressively enough [because they're unaware that FH puts patients at] very high risk for heart disease."

Treatment

The experts interviewed for this article agree that for heterozygous FH patients, who comprise the majority of the FH patient population, statins are the standard first-line treatment for the condition. When children are found to have

FH, they're typically started on statins as young as between the ages of 6 and 8, according to Brown. "Statins as a single drug are the most powerful," he says. "And with the high-dose potent statins that are available now, you can lower cholesterol by 40% to 65%."

Most patients generally tolerate statins well, according to Hopkins, with the occurrence of muscle aches manifesting as the most common side effect; however, these symptoms typically subside shortly after stopping the medication.

But according to Brown, many FH patients need additional treatment on top of statins to effectively manage their cholesterol numbers, so ezetimibe (Zetia) can add another 17% to 20% lowering of the cholesterol.

For patients with homozygous FH or patients with heterozygous FH who can't tolerate statins, another treatment option exists: LDL apheresis. "For homozygous FH patients, they often don't respond well to the drugs since none of their LDL receptors work," Brown explains, "so they often get treated with apheresis."

LDL apheresis is similar to dialysis, Hopkins explains. Patients are connected to a blood-filtering machine that removes LDL cholesterol from the blood. The process takes between two and four hours, Hopkins says, and results in an 80% reduction in LDL cholesterol immediately after the procedure. But because the LDL cholesterol level begins to rise again immediately following the procedure, it's generally repeated every two weeks for heterozygous FH patients and every week for homozygous FH patients.

For insurance to cover apheresis for heterozygous FH patients, Hopkins says that after trying all available treatments as vigorously as is tolerable, patients who don't have coronary disease must have an LDL cholesterol over 300 and, if they have coronary disease, a level over 200.

"The term 'maximally tolerated' therapy is sometimes debatable," Hopkins says, "but generally the most common patients we see for LDL apheresis are those who don't feel good on statins for one reason or another, most commonly muscle aches. Usually the other medications aren't adequate to bring their [cholesterol] levels down to a safe level."

"Optimizing lifestyle by eating a very healthy diet, being physically active, and not smoking—or being exposed to smoke when friends smoke—is also crucial," Block notes. "Rarely, someone will have a liver transplant so that they have cholesterol receptors."

Two new medications, lomitapide (Juxtapid) and mipomersen (Kynamro), recently received FDA clearance for treating homozygous FH patients, and both work to reduce cholesterol production. "These can sometimes be used in addition to LDL apheresis," Brown says, noting the importance of limiting cholesterol production for these patients. "Since the receptors in homozygous FH patients don't work at all, it's hard to increase clearance because you can't do much with bad receptors, but you can reduce the production of cholesterol with these new agents.

"The reason they're approved only for homozygous FH is because they both can cause a buildup of fat in the liver, and we are unsure if that can cause long-term problems as of yet," he adds.

There's currently a third agent being studied that may help heterozygous FH patients, according to Brown, who is an investigator of the drug. "This agent is an antibody to PCSK-9, which is a protein that determines the life expectancy of LDL receptors on the surface of the liver," he says. "When people are given this antibody, it increases the longevity of the LDL receptor on the liver surface by basically turning off the activity of this protein. So the LDL receptor stays on the surface of the liver longer, and that causes more LDL to be taken from the blood, and you can see reductions in LDL cholesterol of up to 60%."

According to Brown, this agent, in the form of an injection given every two weeks or monthly, is particularly promising for heterozygous FH patients who can't tolerate statins. "This has a lot of hope for the future, but studies are still under way to look at safety and tolerability," he says.

Physician Takeaway

According to Brown, the most important concept physicians should grasp is that while high cholesterol likely is a sign of unhealthful lifestyle factors, very high cholesterol likely is related to genetics. This disorder isn't diagnosed nearly enough, he says, for the simple reason that physicians often don't know to look for it. "It's important because many doctors don't know the diagnosis," he says. "They see that patients have high cholesterol, and they treat them for that. So if a patient walks into the doctor's office and their cholesterol's 300, many physicians would be shocked, and they'd start you on medicine.

"But many don't understand the genetics," he adds, and that part is crucial, especially for the offspring of FH patients. "It's the children who are most at risk because they don't get tested early."

First, Brown says physicians always should suspect FH when adult patients present with LDL cholesterol over 190 or children present with levels higher than 170. "Second, they should always screen the relatives, and tell patients to make sure their children and siblings are all screened as well," he adds.

The earlier patients are accurately diagnosed with this silent and outwardly symptomless disorder, the more heart attacks will be prevented, Hopkins says. "Certainly, if you get children diagnosed before their teenage years and get them started on statins, you're going to prevent a lot of heart attacks," he says.

— Juliann Schaeffer is a freelance writer and editor based in Alburtis, Pennsylvania.