Familial Hypercholesterolemia

Rade N. Pejic, MD
Department of Family Medicine, Tulane University School of Medicine, New Orleans, LA

ABSTRACT

Background: Familial hypercholesterolemia (FH) is an autosomal dominant-inherited genetic disorder that leads to elevated blood cholesterol levels. FH may present as severely elevated total cholesterol and low density lipoprotein (LDL) cholesterol levels or as premature coronary heart disease (CHD).

Methods: This review presents information on the disease and on the effects of drug treatment and lifestyle changes.

Results: Routine lipid testing should identify most patients with FH. Once an index case is identified, testing should be offered to family members. Early diagnosis and aggressive treatment with therapeutic lifestyle changes and statins can prevent premature CHD and other atherosclerotic sequelae in patients with FH.

Conclusion: Emerging therapies such as LDL apheresis and novel therapeutic agents may be useful in patients with homozygous FH or treatment-resistant FH. Liver transplantation is the only effective therapy for severe cases of homozygous FH.

INTRODUCTION

Familial hypercholesterolemia (FH), also known as familial hyperlipoproteinemia type 2 or Fredrickson class 2a hyperlipidemia, is an autosomal dominant-inherited genetic disorder that leads to elevated blood cholesterol levels. Typically, the patient inherits only 1 of the defective genes, making him heterozygous. Rarely, the patient inherits an abnormal gene from both parents, making him homozygous; being homozygous for FH causes extremely elevated blood cholesterol levels. Most of the time, a mutation of the low density lipoprotein (LDL) receptor gene is the culprit. However, other genetic mutations have been identified, including those that affect apolipoprotein B (ApoB) structure and proprotein convertase subtilisin kexin type 9 (PCSK9) gain-of-function mutations. The International FH Foundation and the National Institute for Health and Care Excellence (formerly the National Institute of Health and Clinical Excellence) have published recommendations for the detection, evaluation, and treatment of FH to help guide clinicians responsible for treating FH patients.1,2

FH may present as severely elevated total cholesterol and LDL cholesterol (LDL-C) levels or as premature coronary heart disease (CHD). An estimated 5% of myocardial infarctions (MIs) in patients <60 years and 20% of MIs in patients <45 years are attributable to FH.3 Men with FH have a 50% chance of having CHD by the age of 50, and women with FH have a 30% chance of having CHD by the age of 60.3 The homozygous form of FH, although rare, is particularly devastating. In patients with homozygous FH, atherosclerosis develops during childhood, and CHD may appear before the age of 20. Therefore, routine cholesterol screening is recommended at various ages based on risk. The discovery of FH should lead to cascade testing (the systematic method of testing family members) to identify other family members with the condition.

Patients identified as having FH should be counseled about therapeutic lifestyle changes and should take high-dose potent statins to attain 50% LDL-C reductions. Patients with severe FH may benefit from add-on therapy with other cholesterol-lowering medications and LDL apheresis. Children with homozygous FH and extremely elevated LDL-C levels may be candidates for orthotopic liver transplantation.

EPIDEMIOLOGY AND GENETICS

FH is a common genetic disorder with autosomal dominant inheritance. The heterozygous FH form is estimated to occur at a rate of 1:300-1:500.3 However, the homozygous form of FH is quite rare, occurring at
a rate of 1:1,000,000. The genetic founding effect is responsible for FH being more common in Christian Lebanese, French Canadians, and 3 South African populations: Dutch Afrikaners, Ashkenazi Jews, and Asian Indians. In these populations, the incidence of FH may be as high as 1:50-1:100. Based on population studies, the number of patients with FH worldwide is estimated to be 14-34 million.

Presently, more than 1,600 LDL receptor gene mutations cause approximately 85%-90% of FH cases. The Arg3500→Gln mutation in the ApoB gene is thought to be responsible for FH in 5%-10% of cases in Northern European populations. Fewer than 5% of FH cases are a result of PCSK9 gain-of-function mutations.

LDL receptors located on hepatocytes are responsible for clearing LDL-C from blood circulation. LDL receptor gene mutations result in the failure of the hepatocyte to effectively clear LDL-C from blood circulation, leading to higher LDL-C levels and consequently a longer LDL-C half-life. Normally, the half-life of LDL-C is 1.5 days. In heterozygous FH, the half-life increases to 3-4 days, and in homozygous FH the half-life may be as long as 6 days. The 5 major classes of LDL receptor genetic defects are identified in the Table.

Mutations in the ApoB gene are less common than LDL receptor genetic defects. Patients who present with ApoB gene mutations are sometimes referred to as familial defective ApoB patients. In this condition, ApoB has reduced affinity for the LDL receptor because of a single ApoB gene mutation (Arg3500→Gln), leading to an increase in circulating LDL-C levels. However, patients with familial defective ApoB tend to have less severe LDL-C elevations compared to patients with LDL receptor gene defects.

PCSK9 is the enzyme responsible for removing LDL receptors from the hepatocyte surface. Mechanistically, PCSK9 binds to the epidermal growth factor-like repeat A of the LDL receptor. This action initiates LDL receptor degradation. Therefore, gain-of-function mutations involving the PCSK9 gene result in increased LDL receptor degradation. With fewer LDL receptors available, the amount of circulating LDL-C increases. This condition is unusual, representing <5% of FH cases.

### Table. Major Classes of Low Density Lipoprotein (LDL) Receptor Genetic Defects

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDL receptor is not synthesized.</td>
</tr>
<tr>
<td>2</td>
<td>LDL receptor is not properly transported to the cell surface.</td>
</tr>
<tr>
<td>3</td>
<td>LDL receptor does not properly bind LDL cholesterol.</td>
</tr>
<tr>
<td>4</td>
<td>LDL receptor bound to LDL cholesterol does not properly endocytose.</td>
</tr>
<tr>
<td>5</td>
<td>LDL receptor is not recycled back to the cell surface.</td>
</tr>
</tbody>
</table>

Triglyceride levels are relatively normal. Second, patients may have physical examination findings suggestive of FH: arcus corneae, xanthelasma, tendon xanthomas, or tuberous xanthomas. Often, patients or their concerned family members will point out these unusual physical examination findings. Third, patients may present with premature CHD, prompting further evaluation. In this author’s experience, FH is typically detected after routine lipid testing.

According to the American Academy of Pediatrics, primary care physicians should screen children at 2 time points: ages 9-11 and again between ages 17-21. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, all adults >20 years should be screened; although the US Preventive Services Task Force recommends screening men beginning at 35 years of age and women at age 45. In families with known FH or premature CHD, screening should begin as early as age 2. Screening before 2 years of age is not recommended. FH should be suspected in children and young adults when the fasting LDL-C concentration is >160 mg/dL and in adults when it is >190 mg/dL.

Physical manifestations of high cholesterol levels should be further evaluated. Specifically, the presence of tendon xanthomas at any age is suggestive of FH. Tendon xanthomas are palpable nodular tendon irregularities on the extensor tendons of the fingers or along the Achilles tendon. Arcus corneae (also called arcus senilis) in patients <45 years is also a possible indication of FH. Arcus corneae can easily be identified by direct inspection of the cornea. The peripheral cornea will appear opacified. Typically, the opacified cornea is a milky white or blue-gray color. Xanthelasma is a collection of cholesterol deposited under the skin, most commonly seen on or around the upper eyelids. Tuberous xanthomas are larger cholesterol-rich deposits typically found over the joints. When either of these conditions is seen in a
can be identified. Relatives should have their lipids measured or undergo DNA testing if the genetic mutation is known.
against PCSK9, demonstrated LDL-C reductions >75% when added to a statin.\textsuperscript{13} Another PCSK9 monoclonal antibody, alirocumab, demonstrated a 50% LDL-C reduction when used alone.\textsuperscript{14} For patients with severe cases of homozygous FH, liver transplantation is the only effective treatment.

**CONCLUSION**

FH is a common cause of hyperlipidemia and premature CHD. Routine lipid testing should identify most patients with the disorder. However, a thorough family history and a high index of suspicion are needed to identify pediatric patients with the disorder. Once an index case is identified, cascade testing should be offered to family members. Early diagnosis and aggressive treatment with therapeutic lifestyle changes and statins can prevent premature CHD and other atherosclerotic sequelae in patients with FH. Emerging therapies such as LDL apheresis and novel therapeutic agents may be useful in patients with homozygous FH or treatment-resistant FH. Liver transplantation is the only effective therapy for severe cases of homozygous FH.

**REFERENCES**