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My Approach to the Patient With Familial Hypercholesterolemia

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Abstract

Familial hypercholesterolemia (FH), a relatively common Mendelian genetic disorder, is associated with a dramatically increased lifetime risk of premature atherosclerotic cardiovascular disease due to elevated plasma low-density lipoprotein cholesterol (LDL-C) levels. The diagnosis of FH is based on clinical presentation or genetic testing. Early identification of patients with FH is of great public health importance because preventive strategies can lower the absolute lifetime cardiovascular risk and screening can detect affected relatives. However, low awareness, detection, and control of FH pose hurdles in the prevention of FH-related cardiovascular events. Of the estimated 0.65 million to 1 million patients with FH in the United States, less than 10% carry a diagnosis of FH. Based on registry data, a substantial proportion of patients with FH are receiving no or inadequate lipid-lowering therapy. Statins remain the mainstay of treatment for patients with FH. Lipoprotein apheresis and newly approved lipid-lowering drugs are valuable adjuncts to statin therapy, particularly when the LDL-C–lowering response is suboptimal. Monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 provide an additional approximately 60% lowering of LDL-C levels and are approved for use in patients with FH. For homozygous FH, 2 new drugs that work independent of the LDL receptor pathway are available: an apolipoprotein B antisense oligonucleotide (mipomersen) and a microsomal triglyceride transfer protein inhibitor (lomitapide). This review attempts to critically examine the available data to provide a summary of the current evidence for managing patients with FH, including screening, diagnosis, treatment, and surveillance.

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Familial hypercholesterolemia (FH), a relatively common Mendelian genetic disorder, is associated with markedly elevated low-density lipoprotein cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular disease (ASCVD). In patients with untreated FH, life expectancy is significantly shortened, with sudden death and myocardial infarction (MI) as the principal causes of mortality. Timely and effective lipid-lowering treatment improves the life expectancy of patients with FH. Despite the availability of lipid-lowering drugs, most patients with FH do not achieve an LDL-C level less than 100 mg/dL. Newer drugs for FH are now available, however, long-term safety data are awaited. There is a need to develop systematic approaches to identify patients with FH and to conduct cascade screening of their relatives and to increase awareness and control of FH. A significant amount of literature related to the prevalence, undertreatment, and underdiagnosis of FH has accumulated during the past several years. To provide an update on the current evidence for managing patients with FH, we reviewed original and research articles using PubMed and Google Scholar for the following search terms: *familial hypercholesterolemia, FH, prevalence, awareness, pathophysiology, low-density lipoprotein receptor gene, familial defective apoB-100, autosomal recessive, PCSK9, outcomes, aortic stenosis, atherosclerosis, screening, perception, models of care, assessment, registry, healthcare, guidelines, recommendations, statins, ezetimibe, bile acid sequestrants, niacin, lipoprotein apheresis, mipomersen, lomitapide, PCSK9 inhibitors, liver transplantation,* and *gene therapy*. Relevant articles identified were full-text papers in the English, French, German, and Russian languages. The final reference list includes selected research articles as well as relevant reviews that provide additional references.

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AN ILLUSTRATIVE VIGNETTE

A 35-year-old woman is hospitalized with an inferior wall ST-segment elevation MI. Physical examination is remarkable for an early-peaking ejection systolic murmur (grade 2/6) at the left upper sternal border, bruits over the right carotid and subclavian arteries, and yellowish nodules on the tendons of the hands and the Achilles tendon. The lipid profile reveals a total cholesterol level of 338 mg/dL, an LDL-C level of 285 mg/dL, a high-density lipoprotein cholesterol (HDL-C) level of 31 mg/dL (to convert all to mmol/L, multiply by 0.0259), and a triglyceride level of 114 mg/dL (to convert to mmol/L, multiply by 0.0113). Coronary angiography revealed severe triple-vessel disease with right coronary artery occlusion. How should the patient be further evaluated and treated?

HISTORICAL ASPECTS

Familial hypercholesterolemia is a heritable disorder of lipid and lipoprotein metabolism classically transmitted in an autosomal dominant manner and associated with elevated levels of LDL-C. Pathogenic variants in 1 of 3 genes, ie, *LDLR, APOB,* or *PCSK9,* account for most cases. The reason for the relatively high prevalence of genetic variants that lead to FH is not clear, although it is speculated that the variants may have been advantageous from an evolutionary standpoint.[1-3] The first patients with FH were described almost 80 years ago by the Norwegian physician Muller.[4,5] Twenty-five years later, a single-gene codominant inheritance was postulated by Khachadurian[6] based on segregation analysis in Lebanese families. Research relating FH to disorders of LDL-C metabolism by Fredrickson et al[7] and deficiency in a cell surface receptor for LDL by Goldstein and Brown[8] established the molecular basis of the disease. Subsequently, the amino acid sequence of the LDL receptor was determined and the gene was cloned by Russell et al,[9] enabling a catalog of pathogenic variants in the gene.

PATHOGENESIS AND GENETICS

An outline of the molecular basis of FH is presented in Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org). Most of the circulating LDL-C is removed from the blood by hepatic LDL receptor-mediated endocytosis.[8] Pathogenic variants in *LDLR* lead to impaired LDL receptor function and elevated LDL-C levels. A dominant mode of transmission with a gene-dosage effect explains higher cholesterol levels in patients who are homozygous (hoFH) for a mutant allele than in heterozygotes (heFH). Approximately 2000 *LDLR* genetic variants have been submitted to the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk), of which approximately 60% are recognized to be pathogenic. Pathogenic variants in *LDLR* can be broadly categorized as loss-of-function/inactivating/null variants and variants that lead to impaired LDL receptor activity, the former being associated with higher LDL-C levels.[10] Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org) lists genes encoding proteins implicated in the regulation of LDL metabolism.

Patients with pathogenic variants in *APOB* and *PCSK9* may have a less severe clinical presentation than those who have pathogenic variants in *LDLR*. Apolipoprotein B100 functions as a ligand that links the LDL particle to the LDL receptor. Of more than 200 *APOB* variants, only a few are known to impair function and are included in genetic testing panels for FH. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that regulates LDL-C levels by targeting LDL receptor for lysosomal degradation. More than 70 variants in *PCSK9* are associated with interindividual differences in LDL-C levels, with gain-of-function mutations resulting in increased clearance of LDL receptors and increased levels of LDL-C. Recently *APOE*, which encodes apolipoprotein E that directs removal of chylomicron and very low-density lipoprotein remnants from the circulation, has been implicated in the pathogenesis of FH.[11-13] Using family-based linkage analysis and whole exome sequencing, Fouchier et al[14] and Braenne et al[15] identified 5 variants in *STAP1,* which has been proposed as the fourth gene causing FH. Affected individuals had a relatively mild FH phenotype.

Homozygous FH results when a patient inherits a pathogenic variant from each of the heterozygous parents. Culprit variants most often occur in *LDLR* and less frequently in 2 different FH-related genes (double or compound heterozygotes). An autosomal recessive