The Ochsner Journal 14:669–672, 2014

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

Address correspondence to
Rade N. Pejic, MD
Assistant Professor
Department of Family Medicine
Tulane University School of Medicine
1430 Tulane Ave. Mailbox #8033
New Orleans, LA 70112
Tel: (504) 988-4700
Email: rpejic@tulane.edu

Keywords: Genetic diseases–inborn, hypercholesterolemia, hyperlipoproteinemia type II

The author has no financial or proprietary interest in the subject matter of this article.

a rate of 1:1,000,000.[3] 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.[3] 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.[4] 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.[5]

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

Class	Description
1	LDL receptor is not synthesized.
2	LDL receptor is not properly transported to the cell surface.
3	LDL receptor does not properly bind LDL cholesterol.
4	LDL receptor bound to LDL cholesterol does not properly endocytose.
5	LDL receptor is not recycled back to the cell surface.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with FH are typically identified in 1 of 3 ways. First, screening blood work may reveal extremely elevated total cholesterol and LDL-C levels. Patients with heterozygous FH can have total cholesterol levels in the 350-550 mg/dL range. Patients with homozygous FH have total cholesterol levels in the 650-1,000 mg/dL range. In most of these cases, the high density lipoprotein cholesterol (HDL-C) and 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.[6] 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.[7,8] 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

patient <25 years, the patient should be evaluated for FH.

Premature CHD is defined as occurring in men <55 years and women <65 years. In these patients, an underlying cause of their atherosclerotic disease, including FH, should be sought. Lipid testing is best done with a fasting lipid panel. Secondary causes of hyperlipidemia and other contributing factors (ie, diabetes, hypertension, and tobacco abuse) should also be considered. However, if FH is suspected, repeat lipid testing should be performed. In this author's opinion, the physician should assess direct LDL-C quantification or the LDL particle number.

While genetic testing is available and can identify 80% of patients with FH, such testing is typically not done because FH can be diagnosed using validated prediction criteria. The 3 well-known FH predictive models are the Simon Broome Register diagnostic criteria, the Dutch Lipid Clinic Network diagnostic criteria, and the US Make Early Diagnosis to Prevent Early Deaths (MEDPED) diagnostic criteria. If the diagnosis of FH is uncertain but a definitive positive FH diagnosis would affect treatment or genetic counseling, genetic testing should be performed. However, a negative genetic test does not rule out FH with absolute certainty, and the risks of elevated LDL-C must still be addressed. Once a patient is diagnosed with FH, all of his first- and second-degree relatives should have their lipids measured or undergo DNA testing if the genetic mutation is known (cascade testing). From there, additional cases of FH can be identified.

TREATMENT

Patients with FH should be counseled to follow a low-fat, low-cholesterol diet. According to the NCEP ATP III guidelines, no more than 25%-35% of daily calories should come from fat.[7] More important, <7% of daily calories should come from saturated fats. Trans fats should be avoided all together. Cholesterol intake should be limited to <200 mg per day. Patients may also benefit from the addition of 2 g of plant stanols/sterols and 10-20 g of soluble fiber per day. Along with these dietary changes, patients are advised to maintain a normal body weight and avoid smoking tobacco. Aerobic exercise for 30-60 minutes 5-7 times a week with the pulse maintained at 65%-85% of the predicted maximum is also recommended. These therapeutic lifestyle changes may reduce the LDL-C by 10%-15% in addition to improving overall health and physical condition.[9,10]

CHD prediction models, such as the Framingham CHD risk score, should not be used to predict CHD risk in FH patients because they are already at high risk. All patients with FH should be prescribed a high-dose potent statin such as rosuvastatin, atorvastatin, simvastatin, or pitavastatin with the goal of reducing the LDL-C by 50%.[1,2] Because of the lack of clinical trials in FH patients, there are no agreed-upon LDL-C treatment goals, but most experts agree that the LDL-C level should be maintained at <160 mg/dL if possible and even lower (<100 mg/dL) in patients with known CHD.[1,2] According to international guidelines, LDL-C <100 mg/dL should be the goal for most FH patients, and <70 mg/dL is recommended for FH patients with CHD or other major risk factors.[1] However, achieving such levels is frequently not possible with statin monotherapy. Agents such as bile acid sequestrants, ezetimibe, or niacin can be added. In patients with elevated triglycerides, fenofibrate and prescription-strength omega-3 fatty acids (fish oil) may be added. In 2014, an American College of Cardiology/American Heart Association task force published guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. These guidelines do not specifically address the treatment of FH; however, the panel recommends treating adults with LDL-C >190 mg/dL with a high-dose statin.[11] Statins are safe and routinely used in pediatric patients with FH.[12] Children with heterozygous FH can begin treatment at 8 years of age. Children with homozygous FH can begin treatment at 2 years of age. Physicians should not prescribe statins, ezetimibe, or niacin to pregnant and breastfeeding women. If treatment during pregnancy or lactation is necessary, bile acid sequestrants may be used. In severe cases such as homozygous FH or if the patient cannot tolerate statins, LDL apheresis may be used. Homozygous FH patients typically need weekly LDL apheresis. Unfortunately, LDL apheresis is not offered at most hospitals or transfusion centers.

The FDA has approved 2 agents for the treatment of homozygous FH: lomitapide (approved in 2012), and mipomersen (approved in 2013). Lomitapide is an oral agent that inhibits the microsomal triglyceride transfer protein necessary to synthesize the very low density lipoprotein (VLDL) particle in the liver. Inhibition of VLDL synthesis results in reduced LDL-C levels. Mipomersen is a parenterally administered antisense oligonucleotide that binds to ApoB-100 mRNA, preventing ApoB synthesis. Without ApoB, atherogenic lipoproteins including LDL-C particles cannot be synthesized. Lomitapide and mipomersen may cause serious liver injury and are only FDA approved for patients with homozygous FH. Therefore, these drugs can only be prescribed by physicians who complete the FDA-mandated Risk Evaluation and Mitigation Strategy training program.

PCSK9 inhibitors are not commercially available but are in phase 3 clinical trials. A 2014 publication on the efficacy of evolocumab, a monoclonal antibody

against PCSK9, demonstrated LDL-C reductions >75% when added to a statin.[13] Another PCSK9 monoclonal antibody, alirocumab, demonstrated a 50% LDL-C reduction when used alone.[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

1. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolemia from the International FH foundation. *J Clin Lipidol*. 2014 Mar-Apr;8(2):148-172.
2. National Collaborating Centre for Primary Care. Identification and management of familial hypercholesterolaemia (FH). *NICE Clinical Guidelines 71*. London, England: Royal College of General Practitioners; 2008 Aug. http://www.ncbi.nlm.nih.gov/books/NBK53822/pdf/TOC.pdf. Accessed August 11, 2014.
3. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011 Jun;5(3 Suppl):S9-S17.
4. LDLR [database]. University College London; 2007 [modified 2011 January]. http://www.ucl.ac.uk/ldlr/LOVDv.1.1.0/. Accessed May 31, 2014.
5. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolaemia. *Hum Mut*. 1992;1(6):445-466.
6. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011 Dec;128 Suppl 5:S213-S256.
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001 May 16;285(19):2486-2497.
8. U.S. Preventive Services Task Force. *Screening for Lipid Disorders in Adults: Recommendation Statement*. June 2008. AHRQ Publication no.: 08-05114-EF-2. http://www.uspreventiveservicestaskforce.org/uspstf08/lipid/lipidrs.htm. Accessed August 11, 2014.
9. Lichtenstein AH, Ausman LM, Jalbert SM, et al. Efficacy of Therapeutic Lifestyle Change/Step 2 diet in moderately hypercholesterolemic middle-aged and elderly female and male subjects. *J Lipid Res*. 2002;43:264-273.
10. Bruckert E, Rosenbaum D. Lowering LDL cholesterol through diet: potential role in the statin era. *Curr Opin Lipidol*. 2011;22: 43-48.
11. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014 Jun 24; 129(25 Suppl 2):S1-S45.
12. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD006401. doi: 10.1002/14651858.CD006401.pub3.
13. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med*. 2014 May 8;370(19):1809-1819.
14. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week double-blind, randomized Phase 3 trial. *Int J Cardiol*. doi:10.1016/j.ijcard.2014.06.049.

This article meets the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties Maintenance of Certification competencies for Patient Care and Medical Knowledge.