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CASE REPORT

BEGINNER

CLINICAL CASE

DYSLIPIDEMIA

Novel Presentation of Homozygous Familial Hypercholesterolemia With Homozygous Variants in Both LDLR and APOB Genes

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ABSTRACT

This case report describes a 50-year-old-woman from Southeast Asia with extensive atherosclerotic cardiovascular disease, found to have homozygous familial hypercholesterolemia caused by variants of uncertain significance in both the APOB and LDLR genes. Medications were insufficient, and thus LDL apheresis was initiated to further decrease LDL-C. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2019;1:346–9) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The patient is a 50-year-old woman who immigrated to the United States from Southeast Asia in 2010. At age 30, she developed angina and was found to have severe 3-vessel coronary artery disease (CAD) treated with coronary artery bypass grafting (CABG). Three years later, she underwent vein-graft percutaneous coronary intervention in the context of non-ST-segment elevation myocardial infarction (NSTEMI), ultimately requiring redo CABG 6 years following this intervention because of recurrent angina and graft failure. She had no history of diabetes or renal dysfunction and was a lifetime nonsmoker. Her mother and 2 of 4 brothers sustained fatal myocardial infarctions prematurely. Her father and 2 surviving brothers underwent CABG in their 70s and 50s, respectively. Of note, her parents were first cousins.

Her first presentation to a health care professional in the United States was in 2010, at the time of her vein-graft intervention. On a background of atorvastatin 80 mg daily, her total cholesterol was

LEARNING OBJECTIVES

- To consider the Dutch Lipid Clinic Network diagnostic criteria for FH and take into account a patient's vascular history, family history, physical examination, lipid panel, and DNA analysis in formulating the likelihood that a patient has FH.
- To recognize that loss of function mutations in LDLR, APOB, and LDLRAP, or a gain of function mutation in PCSK9, are culpable in the pathogenesis of FH.
- To understand that the consequences of FH are morbid if not detected early. It is estimated that 90% of patients with FH do not know they have the disease. The goal of therapy is to reduce LDL-C to the lowest level possible to prevent ASCVD, which necessitates that lipid-lowering therapies be initiated early. Optimal LDL-C levels are <100 mg/dl in adults or <70 mg/dl in adults with clinical ASCVD and <135 mg/dl in children.

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316 mg/dl, LDL-C 273 mg/dl, triglycerides 86 mg/dl, and HDL-C 26 mg/dl. She subsequently had intermittent contact with the health care system until 2016, at the time of her redo CABG. Atorvastatin was discontinued because of severe myalgias, and evolucumab 140 mg every 2 weeks and niacin 500 mg daily were initiated in late 2017. She was referred to the lipid clinic at our hospital because she was thought to have exhausted all pharmacologic options. Her physical examination was significant for a body mass index of 31 kg/m^2, left Achilles tendon xanthoma (**Figure 1**), bilateral corneal arcus (**Figure 2**), xanthelasma, and multiple xanthomas over the tendons on her hands.

PAST MEDICAL HISTORY

She had peripheral arterial disease complicated by claudication and carotid artery stenosis, for which bilateral endarterectomies were performed. She also had mild aortic stenosis, stenoses of her renal and iliac arteries, and essential hypertension.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for accelerated atherosclerosis beyond uncontrolled acquired risk factors for atherosclerotic cardiovascular disease (ASCVD) primarily includes inflammatory processes and hereditary disorders of lipoprotein synthesis and metabolism. The patient was human immunodeficiency virus negative, never had Kawasaki disease, and displayed no clinical or serologic evidence of an autoimmune condition, making inflammatory processes less likely. Regarding acquired ASCVD risk factors, her hypertension was adequately controlled, and she did not have diabetes, a history of cigarette or illicit substance use, primary biliary cholangitis, or renal dysfunction. Conditions associated with secondary hypercholesterolemia—such as hypothyroidism, nephrotic syndrome, and cholestasis—were not present. Cerebrotendinous xanthomatosis can present with xanthomas, but the patient did not exhibit the neurologic sequelae of this disease. Given her examination findings of bilateral corneal arcus and xanthelasma, coupled with upper and lower extremity tendon xanthomas, extremely elevated LDL-C, and family history of premature CAD, a working diagnosis of homozygous familial hypercholesterolemia (HoFH) was established.

INVESTIGATIONS

The following genes were tested (with the corresponding transcript used for analysis): APOB (NM_000384.2), LDLR (NM_000527.4), LDLRAP1 (NM_015627.2), PCSK9 (NM_174936.3). Testing revealed homozygous variants in LDLR (p.Cys68Arg; c.202T>C) and APOB (p.Thr1941Ile; c.5822C>T), both of which were classified as variants of uncertain significance (VUS) using the American College of Medical Genetics 2015 guidelines. The patient's son and 2 daughters were found to be heterozygous for the above variants. The daughters had an LDL-C of 170 mg/dl and 189 mg/dl (untreated) and were diagnosed with heterozygous FH (HeFH) and treated with atorvastatin and ezetimibe. The rest of the family lives outside of the United States.

MANAGEMENT

The patient was continued on evolucumab 140 mg every 2 weeks and niacin 500 mg daily; ezetimibe 10 mg and rosuvastatin 40 mg daily were added. Mipomersen was not commercially available, and lomitapide was thought to be intolerable while on an extremely fat-restricted diet. Thus, she was referred for LDL apheresis. LDL apheresis was performed using a dextran sulfate column to adsorb ApoB-containing substances per manufacturer protocol (Liposorber LA-15 system, Kaneka Pharma America LLC, New York, New York). Prior to her initial apheresis session, her LDL-C was 378 mg/dl; immediately after apheresis, it was down to 121 mg/dl. She has been undergoing apheresis biweekly, and her pre- and post-LDL-C have been approximately 190 mg/dl and 50 mg/dl, on average, respectively.

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CABG = coronary artery bypass grafting

CAD = coronary artery disease

HeFH = heterozygous familial hypercholesterolemia

HoFH = homozygous familial hypercholesterolemia

LDL-C = low density lipoprotein-cholesterol

LDLR = LDL receptor

NSTEMI = non-ST-segment elevation myocardial infarction

PCSK9 = proprotein convertase subtilsin-kexin type 9

VUS = variants of uncertain significance

American Heart Association, Aetna Foundation, CASCADE FH, Maryland Innovation Initiative, iHealth, Stanford MedX, Nokia, Google, and Apple. Dr. Jones is co-inventor for a method to estimate LDL cholesterol levels, patent application pending. Dr. Martin is co-inventor for a method to estimate LDL cholesterol levels (patent application pending); and has served as a consultant/advisory board member for Sanofi, Regeneron, Amgen, Quest Diagnostics, Akcea, Novo Nordisk, and Esperion. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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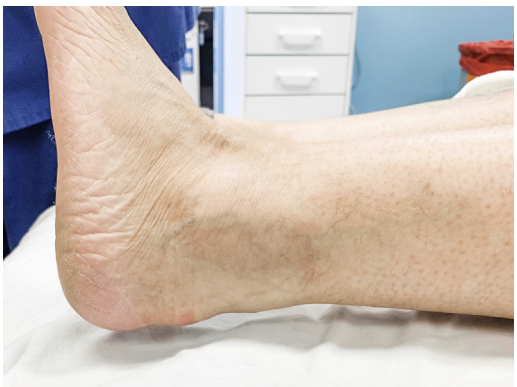
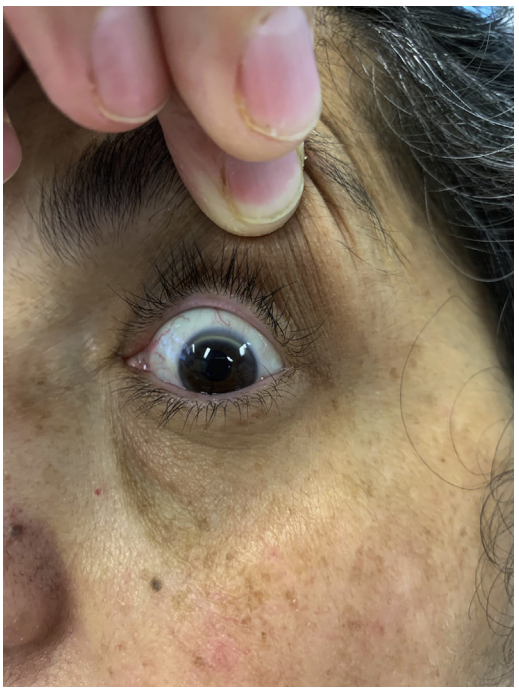
FIGURE 1 Achilles Tendon Xanthoma



A xanthoma is a deposition of cholesterol-rich material in the skin or subcutaneous tissue. They are typically painless and occur in the distal aspect of the tendon. This patient's xanthoma decreased in size following the initiation of LDL apheresis.

FIGURE 2 Superior Corneal Arcus



Arcus is a deposition of lipid in the peripheral corneal stroma. It is not specific for hyperlipidemia and is often seen in the elderly.

DISCUSSION

HoFH was originally characterized as untreated LDL-C >500 mg/dl or treated LDL-C >300 mg/dl and the presence of either xanthomas before age 10 or untreated elevated LDL-C levels consistent with HeFH in both parents (1). The prevalence of HoFH has historically been estimated at 1 in 1,000,000 and HeFH at 1 in 500. However, more recent studies have found that the prevalence of HeFH may be as high as 1 in 200, based on the Dutch Lipid Network criteria, which would suggest that the prevalence of HoFH could be as high as 1 in 160,000 to 300,000 (2). If left untreated, most patients with HoFH develop extensive atherosclerosis before age 20 and die before turning 30.

Familial hypercholesterolemia (FH) is an autosomal codominant disorder, demonstrating both locus and allelic heterogeneity. Loss of function mutations in LDLR, APOB, and LDLRAP—along with gain of function mutations in PCSK9—are culpable in the pathogenesis of FH. In this case, a patient with HoFH was found to have 2 homozygous VUS in genes known to affect LDL metabolism. It is unclear whether one or both variants are pathogenic. Neither variant has been reported in the literature in association with dyslipidemia, and both are rare or absent in the general population (3). The location of the variant in LDLR in the LDLRA domain is significant, as other mutations in this area have been shown to be pathogenic (4). It should be noted that, although unlikely, it is possible that neither variant is deleterious. Regardless of where the mutation occurs, the phenotype is determined by impaired LDL clearance, owing to decreased function of the LDLR or decreased apolipoprotein B-mediated binding of the LDL particle to the LDLR.

Early detection of FH and initiation of lifestyle and pharmacological therapy is crucial to reduce the lifelong burden of LDL-C levels. Systematic cascade screening is needed to ensure that HoFH patients are identified at birth. Also, reverse cascade screening of a patient with HoFH can be used to identify family members with FH. The goal of therapy is to reduce atherogenic lipoprotein burden to the lowest level possible as quickly as possible. Optimal LDL-C is <100 mg/dl in adults or <70 mg/dl in adults with clinical ASCVD and <135 mg/dl in children (5). Statins, ezetimibe, and PCSK9 inhibitors are the cornerstones of therapy, but LDL apheresis may be required to obtain adequate lipid lowering. Liver transplantation as a curative strategy is rarely performed, given its complications and the shortage of donors. Lomitapide and mipomersen are newer agents that affect the production and secretion of

apoB-containing lipoproteins rather than increasing their removal from the bloodstream.

FOLLOW-UP

The patient has continued to receive LDL apheresis biweekly, but she still requires frequent hospitalizations for angina.

CONCLUSIONS

The patient in this case developed HoFH, likely caused by homozygous variants in the APOB or LDLR genes, or both. This case highlights the importance of early detection and treatment of FH and the need for further research into the genetics of the disease.

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KEY WORDS cascade screening, cholesterol, coronary artery disease, Dutch Lipid Clinic, genetics, low-density lipoprotein cholesterol