Familial Hypercholesterolemia (FH) due to an Uncommon LDL Receptor Mutation

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Introduction

Based on improved efforts in primary prevention and education supported by updated lipid goals from newer trial data, low density lipoprotein (LDL) and total cholesterol levels have been trending down for thirty years, yet 69% of adults still have an LDL above 100 mg/dL and severe hypercholesterolemia (LDL > 190 mg/dL) is estimated to exist in approximately 7% of individuals in the US [1]. The majority of these patients have dietary and polygenic hyperlipidemia. Genetic mutations in the LDL receptor, apolipoprotein B (APO B), or proprotein convertase subtilisin/kexin type 9 (PCSK9) are a defining hallmark of homozygous familial hypercholesterolemia (HoFH), a rare but clinically aggressive disease and heterozygous familial hypercholesterolemia (HeFH), a relatively more common but less aggressive disease. These mutations leading to receptor abnormalities result in early and prolonged exposure to extremely high LDL levels, placing patients with HoFH and HeFH at high risk for premature cardiovascular morbidity and mortality relative to non-FH patients [2]. When LDL receptors are low in numbers and/or dysfunctional, patients may also be resistant to statin and other oral antilipemic therapies making it difficult to achieve LDL treatment goals. Unfortunately, with the same LDL elevation, patients with HoFH and HeFH are at a 22 fold higher risk for coronary artery disease compared to a 6 fold higher risk for non-FH patients with the same LDL [1]. Therefore, it becomes important to identify patients with LDL receptor mutations and to treat them aggressively to goal. We present the case of a patient with hypercholesterolemia characterized by a newly described mutation in the LDL receptor.

Case Report

A 33-year-old Hispanic male with a past medical history of World Health Organization (WHO) obesity class I, depression, insomnia, migraine headaches, chronic lower back pain, and post-traumatic stress disorder presented to Endocrinology clinic for consultation for hyperlipidemia. He was incidentally found to have elevated serum total cholesterol and high direct LDL levels. He had been aware of elevated cholesterol levels since the age 26 and was being treated with atorvastatin 80mg daily. His other medications included cyclobenzaprine, fluoxetine, temazepam and ibuprofen. There was no personal history of cardiovascular disease and no family history of hereditary hypercholesterolemia, sudden death, cardiac disease, stroke or other vascular disease in first degree male relatives before age 55 or females before age 60. His Dutch Lipid score was 5 based on his LDL values correlating with possible FH. His total cholesterol of 373 mg/dL (9.6 mmol/L) and LDL of 303 mg/dL (7.84 mmol/L) met Simon Broome diagnostic criteria for FH, although stigmata were absent in the family and the patient’s physical examination did not reveal signs of xanthoma, xanthelasma, heart murmur, carotid or abdominal bruit. His serum lipid panel trending over a 5 year period is shown in Table 1.

Based on the degree of total cholesterol and LDL elevation, lipid subclass analysis (Figure 1) and genetic testing (Figure 2) was performed. The patient was found to have a p(S470C) mutation in the LDL receptor gene leading to substitution of the serine with cysteine residue at position 470. This mutation is located in the EGF-like domain and is associated with dissociation of LDL from the LDL receptor allowing for receptor recycling.

With the adjusted Dutch Lipid Score of 13 and positive genetic testing, the patient was diagnosed with FH based on both Dutch Lipid Criteria and Simon Broome criteria.
Particle subclass analysis revealed an atherogenic pattern (Figure 1). PCSK9 inhibitor therapy was recommended but it was not approved by patient's insurance. He was started on ezetimibe 10mg daily and rosuvastatin 40mg daily and his lipid panel significantly improved with combination therapy as shown in Table 2.

Genetic counseling and evaluation of lipid levels for the patient's family members were also recommended.

**Discussion**

Familial hypercholesterolemia is a common autosomal dominant disorder associated with elevated LDL and premature
atherosclerotic cardiovascular disease. Mutations in the gene coding for the LDL receptor (LDLR) are the most common cause of FH [3] but mutations in apolipoprotein B gene, or proprotein convertase subtilisin/kexin type 9 (PCSK9) genes are also reported. The gene for the LDL receptor is situated on chromosome 19, with 18 exons and is 45 kb long [4]. Nearly 1100 mutations in LDL receptors have been reported in the literature in association with the clinical findings of FH.

This patient has a p(S470C) mutation exchanging serine for cysteine occurring in the EGF-like domain responsible for the dissociation of LDL from LDL receptor affecting receptor recycling. This mutation was reported once previously in a 56-year-old woman of Croatian descent [5]. It is presumed to be clinically significant because the proximity of the new cysteine residue to another unbound cysteine residue (position 452) can lead to the formation of a disulfide bond, and consequent structural alteration of the LDL receptor (Figure 3). However, there are no functional or clinical studies to support the pathogenicity of this variant yet.

Elevated LDL cholesterol in this young patient could result in premature cardiovascular morbidity and mortality, if untreated. Consequently, drug treatment is recommended to effectively reduce his risk. This can be achieved with medications such as statins, ezetimibe and/or PCSK9 inhibitors. PCSK9 inhibitors can decrease LDL cholesterol by 48-71% and total cholesterol by 36-42% through inhibition of PCSK9 binding to LDL receptors, thus increasing the number of LDL receptors available to clear LDL, and lowering LDL cholesterol levels [6].

**Conclusion**

The AACE 2017 Dyslipidemia Guideline [6] categorizes FH patients as being at very high risk for cardiovascular disease and recommends an LDL goal of less than 70 mg/dL. The 2013 American College of Cardiology (ACC) and the American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [7], acknowledges that individuals with FH may not be able to achieve an LDL goal of less than 100 mg/dL and have even more difficulty achieving a goal of less than 70 mg/dL. Those individuals with FH who achieve an LDL of 120 mg/dL or less with 3 cholesterol-lowering drugs should not be considered treatment failures if they have decreased their LDL by 50% or more.

Our patient has a diagnosis of FH based solely on a genetic mutation. His LDL levels have responded well to rosuvastatin and ezetimibe with values falling from 303 mg/dL to 95 mg/dL corresponding to a 68% reduction. This case raises several points. Frequent use of advanced genetic testing for LDL receptor mutations in patients with elevated LDL is likely to identify many more mutations resulting in an increased prevalence of HeFH. Not all patients with genetic LDL mutations causing high total cholesterol and LDL levels demonstrate the same resistance to lipid lowering.
therapy and there is insufficient data available to determine the risk of premature cardiovascular disease in each mutation. Further research is needed to determine LDL goals, treatment strategies and primary prevention in these high risk patients.

References


