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Mini Review

A Brief Review of Familial Hypercholesterolemia

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ABSTRACT

Familial Hypercholesterolemia (FH) is an autosomal codominant disorder characterized by elevated levels of Low-Density Lipoprotein Cholesterol (LDL-C). It manifests in both heterozygous and homozygous forms, most commonly due to loss-of-function mutations in the LDL receptor gene. Lifelong exposure to elevated LDL-C leads to premature and accelerated atherosclerosis, particularly in homozygous individuals. This review summarizes current diagnostic criteria for FH, explores the spectrum of coronary artery involvement, and outlines the expanding therapeutic landscape.

Keywords: Familial hypercholesterolemia; LDL receptor; Coronary artery disease; PCSK9 inhibitors; Early-onset atherosclerosis; Ostial involvement; Evinacumab; Cascade screening

INTRODUCTION

Familial Hypercholesterolemia (FH) is the most common monogenic cause of dyslipidaemia, resulting primarily from impaired LDL metabolism. Persistent elevation of LDL-C levels leads to lipid accumulation in peripheral tissues and promotes premature Atherosclerotic Cardiovascular Disease (ASCVD). The most frequently implicated genetic mutations involve loss-of-function variants in the LDL receptor and apolipoprotein B-100, as well as gain-of-function mutations in PCSK9 molecules [1,2]. Although FH is usually inherited in an autosomal dominant pattern, rare autosomal recessive forms may occur, particularly in cases involving mutations in ApoE or lysosomal acid lipase [1]. Notably, triglyceride and HDL-C levels remain largely unaffected by these genetic mutations.

Heterozygous FH (HeFH) affects approximately 1 in 300 individuals, while Homozygous FH (HoFH) is far less common, with an estimated prevalence of 1 in 400,000 [2]. In HeFH, LDL-C levels typically exceed 190 mg/dL in adults and 160 mg/dL in children. While clinical manifestations in HeFH generally emerge in the fourth or fifth decade of life, HoFH often leads to severe atherosclerotic complications as early as the second decade [3].

LITERATURE REVIEW

Lifelong elevation of LDL-C substantially increases the risk of Coronary Artery Disease (CAD) in FH patients. Importantly, individuals with pathogenic FH mutations face a disproportionately higher risk of CAD compared to those with equivalent LDL-C levels but without such mutations. For instance, loss-of-function mutations are associated with an odds ratio of 9.5 for developing significant CAD [4].

Diagnostic criteria for FH include the US MED PED, Simon Broome, and Dutch Lipid Clinic Network (DLCN) criteria [5], each with its own advantages and limitations. The US MED PED criteria focus on LDL-C concentration and family history. Although simple and cost-effective, this system does not consider physical signs or genetic data. The Simon Broome criteria include clinical features, family history, LDL-C levels, and results from genetic testing, but may fail to detect milder phenotypes and do not distinguish between genotypic variants. The DLCN criteria are widely used and based on a structured point system that incorporates genetic data, with a score above 8 confirming the diagnosis of definite FH [5]. In this system, a functional mutation in LDLR, ApoB, or PCSK9 receives the highest point value, underscoring the diagnostic weight given to genotype [5].

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Clinically, FH may present with angina, myocardial infarction, stroke, or heart failure. Physical findings such as tendon xanthomas, especially over the Achilles and extensor tendons, and arcus juvenilis, a grayish-white corneal ring in young individuals, are highly suggestive of the condition [6]. The Standardized Incidence Ratio (SIR) for cardiovascular complications is particularly high for aortic stenosis (7.9), followed by CAD (4.4), peripheral arterial disease (2.9), aortic aneurysm (2.5), myocardial infarction (2.3), atrial fibrillation (2.0), and heart failure (2.0) [7]. Interestingly, while supravalvular aortic stenosis was once a hallmark feature of FH, the current statin era has seen a phenotypic shift toward valvular aortic stenosis, likely due to lipid infiltration and inflammation akin to the general population [8].

FH patients presenting with myocardial infarction often demonstrate higher SYNTAX scores and more extensive coronary disease compared to non-FH individuals. Common angiographic features include multivessel disease, ostial lesions, diffuse calcification, and bifurcation involvement [9]. These patients also exhibit significantly elevated C-reactive protein levels, indicating a strong inflammatory component to disease progression [9]. Consequently, FH patients face higher rates of Major Adverse Cardiovascular Events (MACE) following Percutaneous Coronary Intervention (PCI). Even after adjustment for confounding factors, the risk of MACE remains approximately twice as high. Notably, younger FH patients presenting with myocardial infarction bear a substantially greater relative mortality risk than their normolipidemic counterparts, a risk that appears attenuated in older FH patients.

At present, there is no consensus regarding the role of exercise testing for detecting silent ischemia in asymptomatic FH patients. Nonetheless, given the propensity for rapid atherosclerotic progression, periodic stress testing may be warranted, especially in patients with a positive family history, to evaluate both ischemic burden and exercise capacity. Similarly, coronary CT angiography offers the advantage of detecting both calcified and non-calcified plaques and may aid in the early identification of subclinical disease. However, the clinical utility of diagnosing and treating asymptomatic CAD in FH remains an area requiring further investigation.

Risk assessment tools such as the Framingham Risk Score and pooled cohort equations are not validated in FH populations and tend to underestimate cardiovascular risk. The International Atherosclerosis Society recommends classifying individuals with LDL-C levels exceeding 400 mg/dL as high-risk, even in the absence of established ASCVD [10]. Without early and effective treatment, patients with HoFH rarely survive beyond the third decade of life and face a threefold higher recurrence rate of coronary events than the general population. Hence, early diagnosis, cascade screening of family members, and aggressive LDL-lowering therapy are paramount.

DISCUSSION

Although LDL-C levels are markedly elevated in FH, lifestyle modifications such as adherence to a heart-healthy diet, regular physical activity, and smoking cessation remain foundational and provide additional benefit [11]. Nevertheless, the cornerstone of risk reduction in FH lies in pharmacological LDL-C lowering, which not only improves angiographic findings but also reduces morbidity and mortality [12]. The American College of Cardiology recommends at least a 50% reduction in LDL-C for HeFH patients, with a target level below 55 mg/dL in those with established ASCVD. Rosuvastatin has demonstrated greater LDL-C lowering efficacy than atorvastatin in this population [13].

Most HeFH patients can achieve target LDL-C levels through a combination of statins, ezetimibe, and PCSK9 inhibitors. Agents such as alirocumab, as demonstrated in the ODYSSEY FH I and II trials, reduce LDL-C by approximately 58% over 78 weeks [14], and are indicated when targets are not met with statins and ezetimibe alone [15]. Bempedoic acid, an ATP citrate lyase inhibitor, has also proven effective in HeFH patients, as shown in the clear outcomes trial [16].

Therapeutic options for HoFH remain limited and less effective. High-dose statins should be initiated early, ideally between the ages of 5 and 8 for adequate response [17]. However, patients with null mutations in the LDL receptor do not respond well to statins and PCSK9 inhibitors. These individuals may require additional interventions such as LDL apheresis, evinacumab, or lomitapide. LDL apheresis physically removes ApoB-containing lipoproteins from circulation and is recommended for patients with LDL-C levels exceeding 300 mg/dL despite six months of maximal medical therapy [17]. Evinacumab, an ANGPTL3 inhibitor, achieved a 47% LDL-C reduction in the ELIPSE trial over 24 weeks [18]. Lomitapide, a microsomal triglyceride transfer protein inhibitor, has been shown to reduce LDL-C levels by approximately 50% in HoFH patients [19].

The management of CAD in FH requires a multidisciplinary heart team approach. While revascularization is standard for acute coronary syndromes, limited data exist to guide management in cases of chronic stable angina. FH patients, particularly children, often have rapidly progressive and anatomically complex coronary disease, including diffuse, calcified, ostial, and multivessel involvement. This complexity poses significant challenges for both surgical and percutaneous interventions. Arterial grafts are preferred over venous grafts due to their superior long-term patency, though their use in children is technically demanding due to small vessel caliber. Percutaneous coronary intervention in pediatric FH patients also carries concerns related to coronary artery growth, stent undersizing, restenosis, and recurrent events.

Given the prolonged asymptomatic phase of FH, early screening is essential. Universal pediatric screening, cascade screening of relatives, and targeted testing in high-risk individuals are all recommended [20]. In recognition of its public health importance, the US Centers for Disease Control and Prevention now includes FH among the three Tier 1 genomic conditions-alongside hereditary breast and ovarian cancer syndrome and Lynch syndrome-for which genetic testing and early identification of mutation carriers have demonstrated clear clinical utility. Imaging studies have shown that approximately one-fourth of adolescent FH patients already exhibit coronary

artery calcium and early aortic lesions, underscoring the role of advanced imaging in identifying subclinical atherosclerosis.

CONCLUSION

Familial hypercholesterolemia remains an underdiagnosed and undertreated condition. Universal pediatric screening and opportunistic testing in appropriate clinical settings are critical for timely diagnosis. Early and aggressive LDL-C reduction, initiated during childhood, provides long-term cardiovascular benefits and significantly reduces the risk of both coronary artery disease and aortic stenosis.

Coronary artery disease in FH tends to be diffuse, calcified, multivessel, and ostial in nature, often necessitating complex and individualized revascularization strategies. Further research is needed to clarify the long-term outcomes of both surgical and percutaneous interventions, particularly in pediatric patients with stable angina, as each modality carries unique limitations in this population. There is a lack of consensus about the role of ischemic testing and CT angiography in asymptomatic FH patients, and further studies are needed to clarify the therapeutic and prognostic implications of identifying subclinical atherosclerosis in these patients.

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