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Familial Hypercholesterolemia: Where Do We Stand?

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Letter to Editor

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Dear Editor

Familial hypercholesterolemia (FH) is a genetically inherited disorder of lipid metabolism characterized by elevated levels of circulating low-density lipoprotein-cholesterol (LDL-C). High levels of LDL-C are associated with an increased risk of premature atherosclerotic cardiovascular events, aortic stenosis, xanthelasma, tendon xanthomas, and corneal arcus due to lipid deposition in various tissues [1]. This autosomal dominant disease, affecting 1 in every 311 to 313 individuals worldwide, is one of the most common genetic disorders and is considered a major source of disabilities, impaired quality of life, and even death [2, 3]. Therefore, addressing this health burden in terms of epidemiology, pathophysiology, diagnosis, prognosis, complications, and management is of crucial importance. If left untreated, FH can lead to a combination of severe complications, ultimately increasing mortality in affected patients [4]. Thus, early and accurate diagnosis of the disease is paramount to prevent suffering caused by severe complications. Regrettably, no international consensus has been reached on a gold standard for FH diagnosis; however, several criteria are currently applied to diagnose suspected individuals. These diagnostic criteria incorporate physical exam findings, personal and family history, and genetic testing [5]. FH is widely underdiagnosed and suboptimally managed in many countries worldwide, particularly in low-income countries. It is estimated that more than 90% of patients with the condition have not yet been diagnosed [6].

Mutations in the LDL receptor, APOB, and PCSK9 account for a vast majority of identified cases of the monogenic inherited form of FH. APOB serves as a ligand for the attachment of the LDL receptor and LDL, and the PCSK9 enzyme is capable of degrading and reducing LDL receptors. Consequently, mutations in these proteins impede LDL-C clearance, thereby inducing hypercholesterolemia [7]. Notably, it is assumed that in at least 20% of patients with the FH phenotype, no defect or mutation in the previously known associated genes is detected [6]. Polygenic causes are speculated to be responsible for mutation-negative patients [8]. Nevertheless, genetic testing could be a viable option for clinically suspicious individuals, considering the high cost of non-statin medications. Therefore, cascade screening through genotyping and serological testing (particularly in children between the ages of 1 to 9) should be conducted to minimize the risk of undiagnosed cases. Importantly, universal plasma LDL-C screening is an effective step towards identifying affected patients. Given the high cost of genetic testing and resource requirements, widespread use in low-income countries may not be feasible; insurance reimbursement and facilitation strategies by

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the healthcare system in this regard could be quite helpful.

In addition to genetic and serological testing, non-invasive imaging, specifically computed tomography or carotid ultrasound, may be beneficial for the detection and evaluation of coronary calcification and its extent [9]. Furthermore, obtaining a detailed and accurate personal history for claudication, angina, previous myocardial infarction, transient ischemic attack, and arterial revascularization, along with a comprehensive physical exam, should not be overlooked [10]. Physicians should be cognizant of the secondary causes of hypercholesterolemia or the consumption of drugs that may have led to elevated levels of LDL-C [9, 11].

Treatment varies depending on the stage, severity, and genotype of the disease, but generally, the following medications are used for the management of FH: statin, ezetimibe, bile acid sequestrants, niacin, PCSK9 inhibitors, lomitapide, mipomersen, LDL-C apheresis, and finally, liver transplantation for young patients with homozygous FH and rapid progression of the disease or its complications. These medications should be complemented by a healthy diet, exercise therapy, weight loss, and smoking cessation [10]. Follow-up and monitoring of patients through the measurement of carotid intima-media thickness, assessment of pancreatic and biliary function, and examination for the typical signs and complications of the disease are of immense benefit to evaluate the efficacy of the medications and track the progression of the disease [12].

In conclusion, rigorous strategies should be implemented to:

- Identify undiagnosed patients through serological lipid screening.
- Detect asymptomatic individuals through cascade genomic screening.
- Routinely follow up and monitor confirmed cases, suspicious cases, and their relatives.
- Encourage asymptomatic or high-risk individuals for FH to take precautions against the disease and its devastating complications through patient education and lifestyle modifications.
- Select the appropriate medications for each patient and consistently assess the effectiveness of the therapy to switch the medications at the proper time.

In general, an appropriate diagnosis, screening, follow-up, and management of FH require the simultaneous and concerted efforts of a cardiologist, endocrinologist, nurse practitioner, genetic counselor, and medical geneticist in a multidisciplinary team. This approach aims to further elucidate the status of the disease and enhance the quality of life in affected patients.

Conflict of Interests

None.

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