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Familial hypercholesterolemia: clinical pearls

Abstract

Familial hypercholesterolemia is an important cause of premature cardiovascular disease. A defect in low-density lipoprotein (LDL) metabolism results in extremely elevated levels of LDL-cholesterol. Although it was one of the most common genetic disorders, it is frequently underdiagnosed or inappropriately treated. Current advances in LDL lowering therapies have made a great promise in treating familial hypercholesterolemia. Early recognition and optimal control of LDL levels are crucial in preventing its atherosclerotic burden. A multi-disciplinary approach is needed to provide optimal care for patients with familial hypercholesterolemia. In this clinical paper, we outline the current knowledge about screening, diagnosis, and management of familial hypercholesterolemia.

Keywords: familial hypercholesterolemia, inherited dyslipidemia, atheroscelorsis, cardiovascular disease, premature myocardial infarction, primary prevention

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Yousif M Hydoub,[1] Seema Nour[2]

[1]Department of medicine, Mafraq Hospital, United Arab Emirates

[2]Department of cardiac sciences, Sheikh Khalifa Medical City, United Arab Emirates

Correspondence: Yousif M Hydoub, Mafraq Hospital, Bani Yas, Abu Dhabi, United Arab Emirates, Email yomohamed@seha.ae

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Abbreviations: FH, familial hypercholesterolemia; LDL, low-density lipoprotein; CV, cardiovascular; ApoB-100, apolipoprotein B-100; PCSK9, proprotein convertase subtilisin/kexin type 9

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder that results in a disturbance in the metabolism of low-density lipoprotein cholesterol (LDL). It affects both adults and children, depending on genotypic features. FH, especially if untreated, results in devastating cardiovascular (CV) morbidity and mortality.[1,2]

Etiology

FH, in its commonest type, is due to an autosomal dominant defect in the genes encoding for proteins involved in LDL metabolism. There are autosomal recessive variants, but these are much less common.[3] Patients can have a homozygous or a heterozygous defect, which will determine the severity of the disease and the age of onset of CV disease manifestations. The three main genetic defects that lead to FH are defects in the LDL receptor gene (most common), apolipoprotein B-100 (ApoB-100) gene[4], and proprotein convertase subtilisin/Kexin type 9 (PCSK9) gene.[5] These three mutations account for 60 to 80 percent of patients with definite FH.[6] Other mutations, like the signal-transducing adaptor family member 1 (*STAP1*) gene mutation, have been reported to be associated with FH.[7]

Epidemiology

The prevalence of FH varies depending on the population studied and the criteria used for diagnosis. Homozygous FH is relatively rare with a reported prevalence of 1 in 300,000 individuals.[8] Homozygous FH is much more common, yet underdiagnosed, with a prevalence of 1 in 250 to 1 in 500 individuals.[9,10] The prevalence is higher in obese individuals. There is no reported sex predilection, but a variation among races with African Americans having the highest reported prevalence in the NHANES study.

Pathophysiology

There are multiple genetic mutations that lead to the phenotypic features of FH. The end-result in all pathways is the dysfunctional binding of LDL receptors to the LDL cholesterol, thereby decreasing the uptake and destruction of LDL cholesterol in the liver and the resultant rise in serum LDL levels. One of the most common and well-studied mutations is due to numerous "loss of function" mutations in the gene encoding for the LDL receptor protein on chromosome 19.[11] A less common mutation is one that encodes for ApoB-100, a protein on the LDL receptor that binds to the LDL cholesterol. In the last twenty years, or so, a new "gain of function" mutation in the PCSK9 gene was found to be highly associated with familial hypercholesterolemia. [12–14] PCSK9 proteins binds to the LDL receptor, which results in internalization of the LDL receptor, thereby reducing the number of expressed receptors available to bind LDL cholesterol.

Symptoms and signs

Homozygous FH typically manifests in childhood. Findings include xanthelasmas and xanthomas in the skin, joints, ears, tendons, and other sites. Patients with heterozygous FH are usually asymptomatic, but xanthomas start to develop by the third decade of life. Arcus cornealis before the age of 45 is also common. Symptoms of coronary heart disease (e.g. angina, myocardial infarction, and heart failure), aortic stenosis, cerebrovascular disease, and peripheral arterial disease are common manifestations.

Evaluation

Diagnostic criteria

The two most commonly used criteria for evaluation and diagnosis of FH are the Dutch lipid clinic criteria and the Simon Broome criteria.[15,16] Both incorporate LDL levels, presence of xanthomas, presence of a genetic mutation or family history of FH, premature cardiovascular events, tendinous xanthomas and/or arcus cornealis and elevated LDL levels in young ages. The Dutch lipid clinic criteria categorize patients into definite, probable, possible or unlikely FH, while the Simon Broome classifies patients as definite or possible. Having only an LDL level of 330 mg/dl or more, or a mutation in the LDL receptor, ApB-100 or the PCSK9 gene will earn a diagnosis of probable FH, based on the Dutch lipid clinic criteria. If a patient has any of the additional factors of the Dutch lipid clinic, on top of the gene mutation or the above-mentioned LDL level, the diagnosis

becomes definite FH. Based on the Simon Broom criteria, a diagnosis of definite FH requires an LDL level of at least 155 mg/dl and a gene mutation or tendinous xanthomas in the patient or first- or second-degree relatives.

Cascade screening

Because FH is a common and frequently unrecognized genetic disorder, cascade screening is recommended.[17,18] Once a patient is diagnosed with FH. All first-degree relatives should be screened. If a new case of FH is diagnosed during screening, all first-degree relatives of the new proband should be screened and so forth. Screening methods include, preferably, genetic testing and/or lipid tests.

Treatment

Approach to therapy

A holistic approach should be sought in the treatment of FH. Besides lowering LDL levels, control of the patient's lifestyle risk and other modifiable risk factors of coronary heart disease is essential in reducing CV morbidity and mortality in patients with FH. Setting a suitable target LDL level is difficult, as patients with FH present with varying degrees of elevated LDL levels. Most guidelines recommend a reduction of 50% or more of the initial untreated LDL level, in patients with FH.[19,20] Some guidelines consider patients with prior coronary heart disease or concomitant diabetes are considered high risk and are recommended to have an LDL level below 70 mg/dL, while patients without prior coronary heart disease or diabetes are considered low-moderate risk and have recommended target LDL level below 100 mg/dL. LDL levels should be checked every 2-3 months, while on treatment, to adjust drug therapies accordingly.

Drug therapies

Statins are the gold standard therapy for FH. All guidelines recommend statins as first-line drugs for patients with FH, with a goal of reaching maximally tolerated doses.[21] The effect of statins has been well studied and most randomized clinical trials observed a reduction of around 50 percent of the initial untreated LDL levels, as well as a reduction in cardiovascular events.[22–24] Unfortunately, a large number of patients with FH, on maximally tolerated statins alone, either do not show this level of reduction in LDL levels, or they do not reach their goal LDL levels, even with a 50 percent reduction, because their initial LDL levels are so high. Second-line therapies include ezetimibe and PCSK9 inhibitors. Ezetimibe has been showing to add an extra 10 to 30 percent reduction in LDL levels for patients on maximally tolerated statins.[25,26] Currently, ezetimibe is the drug of choice as second line in most guidelines.[27,28] PCSK9 inhibitors have shown a great reduction in LDL levels and cardiovascular outcomes in different randomized clinical trials.[29,30] In those trials, PCKS9 inhibitors lowered LDL levels by 50 to 60 percent. While exhibiting higher efficacy than ezetimibe, the use of PCSK9 inhibitors is limited by their high costs and the reluctance of insurance companies to approve their use.[31] Hence, PCSK9 inhibitors can be used as second or third-line drugs for patients with FH. Fourth line therapies include mipomersen, lomitapide, LDL apheresis, ileal bypass surgery, and liver transplantation.[32–35] These are usually reserved if the LDL does not reach the target level with the use of statins, ezetimibe and PCSK9 inhibitors.

Prognosis

Patients with homozygous FH have a poor prognosis. They usually die before the third decades of life from CV events.36 Patients with heterozygous FH are usually asymptomatic until the third decade of life. After that, their risk of premature cardiovascular events increases exponentially.

Consultations

Consultation with a lipid specialist is recommended whenever LDL cholesterol is above goal, with maximally tolerated statins and ezetimibe.[37]

Clinical pearls

a. FH is a common cause of premature cardiovascular events in children and adults

b. Various diagnostic criteria of FH are available online and can help direct further workup

c. Heterozygous FH is under recognized and commonly treated sub-optimally

d. Cascade screening of first-degree relatives of patients with FH is essential in primary prevention of CV events

e. Referral to a lipid specialist can help optimize the control of LDL hypercholesterolemia in patients with FH

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None.

Conflicts of interest

None declared.

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