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A Brief Update on Familial Hypercholesterolemia

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Abstract

Type II Familial Hypercholesterolemia (FH) is the autosomal dominant disorder of lipid metabolism. It is identified by very high Low-Density Lipoprotein Cholesterol (LDL-C) levels because of a gene mutation causing premature coronary heart disease. Homozygous individuals typically acquired disease in childhood. Most of the cases are undetected and hence undiagnosed and sub-optimally treated. Thus, early diagnosis and proper treatment protocols are necessary in preventing premature death of such individuals.

Keywords: Familial hypercholesterolemia; Genetics; Etiology; Treatment; Management

Abbreviations: LDL-C: Low-Density Lipoprotein Cholesterol; LDLR: Low-Density Lipoprotein Receptor; APOB: Apolipoprotein B-100 Gene; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9 Gene; HeFH: Heterozygous FH; HoFH: Homozygous FH; CNVL: Copy Number Variation; GOF: Gain of function; LOF: Loss of Function; MED-PED: Make Early Diagnosis to Prevent Early Deaths; NICE: National Institute for Health and Clinical Excellence; LA: LDL-C Apheresis; MTP: Microsomal Triglyceride Transfer Protein; ASO: Apob Antisense Oligonucleotide

Introduction

Genetic disorders with high Low-Density Lipoprotein Cholesterol (LDL-C) are mostly caused by autosomal dominant conditions. Here, one copy of an altered gene in each cell is sufficient to cause the disorder, and rarely inherited as a recessive trait. Individuals with this genetic disorder can either be heterozygous or homozygous, with the latter being rarer. 80% to 90% of clinical FH cases are caused by mutations in the Low-Density Lipoprotein Receptor (LDLR) and possess an autosomal dominant inheritance. In addition, mutations in Apolipoprotein B-100 Gene (APOB) involved in LDLR binding, and proprotein convertase subtilisin/kexin type 9 gene (PCSK9) involved in cholesterol metabolism, can cause autosomal dominant heterozygous hypercholesterolemia, but they are less common [1-5]. Typically, afflicted individuals inherit one mutated copy of the gene from one affected parent and one normal copy of the gene from the other, which is referred to as Heterozygous FH (HeFH). However, a person with familial hypercholesterolemia may rarely have a mutation in both copies of the LDLR, APOB, or PCSK9 genes. This happens when both parents have familial hypercholesterolemia and each pass on one mutated copy of the gene to their children, which are referred to as Homozygous FH (HoFH). There is a "gene dosing effect", meaning homozygotes are affected more severely than heterozygotes. The occurrence of two mutations causes a more severe type of familial hypercholesterolemia, which typically manifests in childhood [6]. HeFH has a prevalence of 1:300, making it the most common monogenic, autosomal dominant disorder in humans. Incidence of FH is higher in some small sub-populations across the world, such as Christian Lebanese, Dutch Afrikaners, French Canadians, Ashkenazi Jews, and some groups in Tunisia. In contrast, individuals with HoFH are rare; this disorder occurs in approximately one in 160,000 to 500,000 people [7].

Etiology

Low density lipoprotein receptor (LDLR) defect

This receptor is responsible for elimination of low-density lipoprotein (LDL) from the blood. Any defect in this receptor can lead to abnormal accumulation of LDL. LDL receptor genetic defects include [8,9].

a) insertion

b) large-scale DNA copy number variation (CNV) [10]

c) non-sense and mis-sense mutations

d) splicing mutations

e) deletion

Table 1: Mutations in LDLR are classified into.

Class I	Null protein synthesis
Class II	Partially or completely retained in the endoplasmic reticulum
Class III	Binding defect and are not able to properly interact with ApoB apolipoprotein
Class IV	Impaired endocytosis
Class V	Affect the recycle mechanism and LDLR cannot be recycled back to the membrane

Apolipoprotein B (APOB)

This type of FH is also called familial defective APOB in which mutation occurs in exons 26 and 29 [11]. As a result, there is a decrease in binding capacity of LDLR, the level of LDL in the blood increases, but lower than LDL level in LDLR genetic defect.

Protein Convertase Subtilisin/Kexin 9 (PCSK9)

PCSK9 variant divided into:

a. Gain of function (GOF): this variant can lead to increment in LDL level, due to increment in LDLR degradation which leads to decrease in LDL uptake, that eventually leads to high level of circulating LDL [12].

b. Loss of function (LOF): associated with lower LDL-C levels and reduced cardiovascular disease.

LDL receptor adaptor protein 1 (LDLRAP1)

Mutation in this protein leads to inhibition of LDL uptake [13].

Signs and Symptoms

Adults and children that have type II familial hypercholesterolemia have very high levels of low-density lipoprotein (LDL) cholesterol in their blood. LDL cholesterol is considered as bad cholesterol because it can build up within the walls of the arteries to make it hard and narrow. Too much of cholesterol is typically placed in specific portions of the skin and a few tendons around the iris of the eyes.

a) Skin: The most frequent spots for cholesterol deposits to occur on the hands, elbows, and knees. They can also occur in the skin around the eyes.

b) Tendons: Cholesterol deposits may thicken the Achilles tendon, alongside some tendons within in the hands.

c) Eyes: High cholesterol levels can be caused by corneal arcus. This happens mostly in older people but can also occur in younger people who have type II FH.

Evaluation

Secondary causes of hypercholesterolemia such as hypothyroidism, nephrotic syndrome and liver illness must be ruled out by history and laboratory testing. In most circumstances, FH is diagnosed as follows:

a) Clinical, as evidenced by a personal history of early CAD and a familial history of early CAD (definite MI or sudden death and in younger age)

b) Results of a physical examination (tendon xanthomas and premature corneal arcus)

c) Lipid levels that are too high (LDL-C more than 190 mg/dL)

Previously, the diagnosis was mainly made during an acute MI in a young individual. However, it is currently most usually discovered by normal lab testing, which displays high LDL-C, leading to clinical suspicion. Triglyceride levels are typically acceptable; however, HDL levels may be low. It is critical to underline that any LDL-C level more than 190 mg/dL should prompt a search for HeFH or HoFH [7]. In most situations, FH is diagnosed phenotypically (Figure 1 & 2). The Dutch Lipid Clinic Network criteria, Simon Broome criteria, Make Early Diagnosis to Prevent Early Deaths (MED-PED) criteria, and Japanese FH criteria are available clinical tools for FH diagnosis. Index cases could be identified through targeted screening of individuals with premature CVD, opportunistic screening in primary care based on age and gender-specific plasma LDL-C levels, or universal screening based on age and gender-specific plasma LDL-C levels before the age of 20 and ideally before puberty. Children with xanthomata or other FH-related physical abnormalities, as well as those suspected of having HoFH based on family history, should be examined at the age of two. Between the ages of 5 and 10 years, children suspected of having HeFH should be tested. In children and adolescents, it is advised that two fasting LDL cholesterol levels be obtained. LDL more than or equal to 155 mg/dL or greater than or equal to 135 mg/dL with a parental history of hypercholesterolemia or early CHD indicates a significant likelihood of FH [7]. Testing should not be performed during severe sickness since it might reduce LDL-C levels, resulting in false-negative results. If an individual is currently taking statins, it's a good idea to check at LDL-C levels before starting. If the LDL-C level is not known, it should be calculated based on the dosage of the specific statin. Because FH is a lifelong coronary risk equivalent, cardiovascular risk assessment techniques such as the Framingham risk score should not be employed Table 1. In asymptomatic individuals with FH, cardiac CT and carotid ultrasonography may be effective for risk stratification, but further research is needed [7]. The following criteria are used to make a clinical diagnosis of homozygous FH:

a. Untreated LDL-C >500 mg/dL (>13 mmol/L) or treated LDL-C ≥300 mg/dL (>8 mmol/L)

b. Cutaneous or tendon xanthoma before ten years of age

c. Elevated LDL-C levels consistent with heterozygous FH in both the parents

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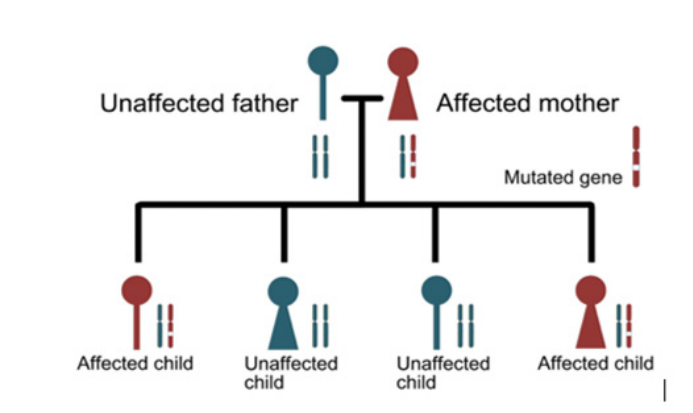

Figure 1: Autosomal dominant inheritance pattern of HeFH.

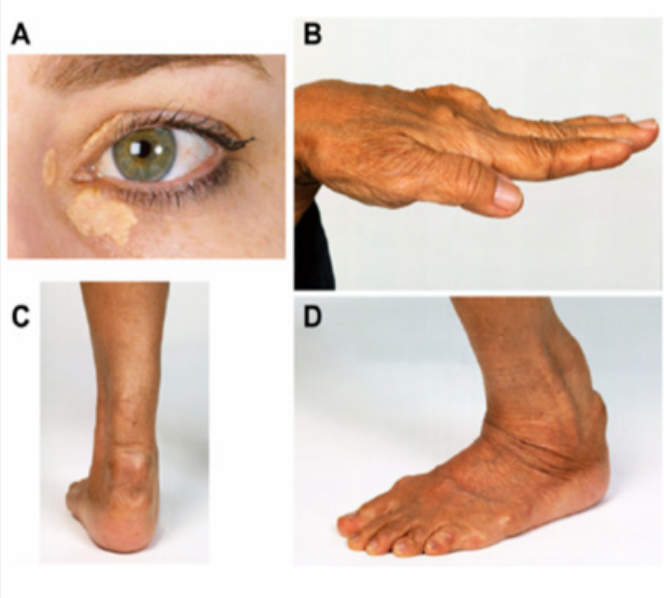

Figure 2: Physical signs of HeFH, which result from deposited cholesterol in skin, tendons, and eyes. A: Xanthelasma and corneal arcus. B: Xanthomas in wrist tendons. C: Thickened achilles tendon. D: Xanthomas in feet tendons.

A comprehensive family history is essential for detecting familial hypercholesterolemia. Doctors will want to know whether any of the siblings, parents, aunts, uncles, or grandparents had had high cholesterol or heart disease in the past, especially when they were younger. When physical examination is conducted, doctors look at the skin around the hands, knees, elbows, and eyes for cholesterol deposits. Tendons in the heel and hand may thicken, and the iris of the eye may acquire a grey or white ring. The Dutch Lipid Network Criteria is one of the most extensively used clinical scoring methods for diagnosing FH (DLNC)The DLNC calculates a score based on clinical factors such as cholesterol levels, physical examination, and family history, as well as genetic data if available. A score of higher than 8 shows a "definite" FH. It is important to note that genetic criteria are not necessary for a diagnosis. Another set of criteria is the Simon Broome Registrar Criteria, which uses both clinical and genetic data. A third set of criteria, the Make Early Diagnosis and Prevent Early Death (MED-PED) criteria, focuses on lipid levels and family history rather than genetic testing. These three clinical criteria have been examined, and none have been shown to outperform the others. When patients in the "definite" group in each of the criteria were genetically examined, the detection rate of mutations was as low as 30-40%. These data suggest that not all mutations were discovered and that polygenetic influences were maybe overlooked. As a result, the phenotype may be more important than the genotype in making a diagnosis and justifying therapy. The International Atherosclerosis Society concurred, highlighting the significance of LDL-C levels and preclinical disease in FH [14].

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Genetic testing

Genetic testing is considered the standard for diagnosing FH. Some studies have found that a gene positive individual has a greater risk of cardiovascular disease than a gene negative individual at any LDL-C level. Because certain mutations are associated with greater risk, genetic testing may be able to explain phenotypic variation [14]. Once an individual has been diagnosed with FH (either with or without the use of DNA testing), a process known as "cascade screening," "cascade testing," or "family screening" (step-by-step testing of close relatives) is recommended to identify those with FH before symptoms appear, allowing for early and intensive treatment and the prevention of disease and death. If a pathogenic variant is found, DNA testing can be used to determine the risk among the patient's first-degree relatives (parent, sibling, child) and, if necessary, more distant relatives. If DNA testing is not available, a cholesterol-based variation of cascade screening can be used instead. Cascade screening, done in any way, has been found to be useful in identifying people with FH who were not being treated properly. A genetic counsellor can assist a family in this endeavour [15]. Cascade screening has been proved to be cost-effective in multiple trials, and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom has endorsed it. Cascade screening of relatives of persons with FH is considered a "Tier 1 application" by the Office of Public Health Genomics at the Centers for Disease Control and Prevention, which implies that there is excellent evidence that its implementation will prevent disease and save lives. Planar xanthomas, corneal arcus, and extremely high total and LDL-C are all symptoms of HoFH in Newborns and young children; LDL-C is greater than 400 mg/dL. The parents are "obligate heterozygotes," which means they have HeFH until it is proven differently [15].

Treatment Plan and Management

It is important to guide patients on lifestyle modifications and to correct all adjustable non-cholesterol risk factors. A healthy diet, exercise therapy, stop smoking, and management of obesity add to important lifestyle management of the disease. Pharmacological options as addition to lifestyle modification for reaching these goals are high-intensity statin therapy, bile acid sequestrants, ezetimibe, fibrates and niacin. Statins are first-line drugs for the control of FH but may not be effective in HoFH as they are reliant on increasing LDLR expression for lowering LDL-C. LDL-C levels are the main target for treatment in FH patients. Beginning with high-intensity statins in FH adults and including ezetimibe or other therapies when treatment goals are not attained is advised. In adults, the target for LDL-C therapy will be at least 50% reduction, followed by LDL-C less than 70 mg/dL (no CHD or other major risk factors), or less than 55 mg/dL (in the existence of CHD or other major risk factors). In numerous cases, it is hard to attain these goals. In children with FH, ages 8 to 10 years, following the establishment of dietary changes, if LDL-C is greater than 155 mg/dL on two occasions, low dose statin monotherapy should be advised for an LDL-C goal of lower than 155 mg/dL. In children with FH, over the age of 10, after the institution of dietary changes, if LDL-C is more than 135 mg/dL on two occasions, statin monotherapy should be advised for an LDL-C goal of lower than 135 mg/dL, with the inclusion bile acid sequestrant or ezetimibe if needed [7]. In HeFH, statin monotherapy can reduce LDL-C up to 30 to 60 percent and an extra 20 to 30 percent lowering can be attained by combination therapy. Lipid-lowering with a statin-based process has been revealed to enhance survival and lower morbidity notably. PCSK9 inhibitors can be helpful as long as some LDLR function is there; the FDA accepts alirocumab and evolocumab for use in adult patients with clinical ASCVD or HeFH needing more LDL-C lowering as an addition to diet and maximally allowed statin therapy. Evolocumab is presently FDA-approved for HoFH as an addition to diet and other LDL-C lowering therapies.

The presence of other ASCVD risk factors will involve larger intensity of medical control. Even though proof for combination therapies for the prevention of ASCVD events is missing, strict control of LDL-C levels is advised in patients with FH [7]. HoFH is less reactive to drug therapy than HeFH, so LDL-C apheresis (LA) has been developed as a primary control strategy. More options for patients with HoFH are the Microsomal Triglyceride Transfer Protein (MTP) inhibitor, Apob Antisense Oligonucleotide (ASO) and lomitapide, mipomersen, especially when LA is not accessible. As a result of their mechanism of action, these drugs do not rely on LDLR expression for lowering LDL-C. In women of childbearing possibility, advice on contraception before beginning a statin and pre-pregnancy counseling is essential. Statin therapy should be stopped 3 months before planned conception and should not be utilized at time of breastfeeding or pregnancy. Lipid-lowering therapy apart from bile acid sequestrants should not be used at the time of pregnancy. LDL apheresis has been carefully used during pregnancy and is mainly useful in patients with confirmed CAD. LDL-C apheresis as an addition to diet and maximally allowed drug therapy should be thought about in all patients with HoFH or compound HeFH, in HeFH with CHD not attaining LDL cholesterol goals on maximal drug therapy or in the setting of statin intolerance. In children with HoFH, LA should be thought about before the age of 5 and not more than 8 years. LA meetings usually last 2 to 4 hours and are done on a weekly or bi-weekly plan at apheresis centers. It reduces LDL and Lp (a) levels by 50% to 75%, and over 1 to 2 weeks, levels tend to return to baseline. In chronic utilization of LA, LDL and Lp (a) levels may be decreased by 20% to 40%. FDA accepted signs for LA are LDL-C more than 300 mg/dL on maximally accepted therapy, and in the existence of CAD, LDL-C more than 200 mg/dL on maximally accepted therapy. Price and access to LA are barriers, consequently restricting options in the effective management of patients with homozygous FH. Orthotopic liver transplantation is considered for young patients with HoFH with fast development of atherosclerosis or aortic stenosis if they are not able to endure LA or have insufficient LDL-C lowering with diet, LA and medications [7].

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Conclusion

In summary, type IIa hypercholesterolemia, also known as familial hypercholesterolemia, is one of the most common monogenic, autosomal dominant disorders in humans. It's a genetic disorder that is passed down through families which causes severely elevated LDL cholesterol levels that can cause atherosclerotic plaque formation in the coronary arteries and proximal aorta at a young age, increasing the risk of cardiovascular illness. One of the most common symptoms of FH is cholesterol depositions (xanthomas) within the tendons of elbows, hands, knees, and feet. An estimated 80-90 percent of FH is caused by a pathogenic heterozygous mutation in one of three genes (APOB, LDLR, PCSK9). The Dutch Lipid Clinic Network criteria, Simon Broome criteria, Make Early Diagnosis to Prevent Early Deaths criteria, and Japanese FH criteria are available clinical tools for FH diagnosis. Index cases could be identified through targeted screening, opportunistic or universal screening in primary care based on age and gender-specific plasma LDL-C levels, ideally before puberty. Once an individual has been diagnosed with FH (either with or without the use of DNA testing), a process known as "cascade screening," "cascade testing," or "family screening" (step-by-step testing of close relatives) is recommended to identify those with FH before symptoms appear, allowing for early and intensive treatment and the prevention of disease and death. Criteria used to diagnose FH are extreme hypercholesterolemia (LDL-C levels above 190mg/dL), history of premature CAD, physical examination (xanthomas/corneal arcus), and a family history of symptoms indicative with FH.

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