GENOMIC MEDICINE: CLINICAL PRIMER
https://doi.org/10.33591/sfp.50.1.u2

Unit No. 2

FAMILIAL HYPERCHOLESTEROLAEMIA: SAVING LIVES THROUGH EARLY DETECTION AND INTERVENTION

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ABSTRACT

Familial hypercholesterolaemia (FH) is a common genetic disorder associated with premature cardiovascular disease caused by excessive accumulation of cholesterol since childhood and adolescence. While homozygous FH presents in childhood with physical signs of cholesterol deposition, heterozygous FH is often "silent", un-diagnosed, and often diagnosed in adulthood when a third of patients would already have developed cardiovascular disease (CVD). Genetic testing and subsequent cascade screening of families of affected individuals is critical in detecting FH early, allowing for early initiation of effective lipid-lowering treatment.

SFP2024; 50(1): 17-22

Key words: Heterozygous, homozygous, cardiovascular, cascade screening, hypercholesterolaemia

INTRODUCTION

Familial Hypercholesterolaemia (FH) is a common, monogenic disorder that affects one in 140 individuals in Singapore[1]. FH is characterised by early, cumulative elevation in low-density lipoprotein cholesterol (LDL-C), leading to premature atherosclerotic cardiovascular disease (ASCVD). The risk of ASCVD is very high in untreated individuals, with 50 percent of men and 30 percent of women developing coronary artery disease by age 50 and 60 respectively, causing excess mortality especially in young adults.[2,3] In contrast, the median age of onset for myocardial infarction in the general population in Singapore is 70 years.[4] Early detection and treatment with lipid-lowering therapy reduces the ASCVD risk to near that of the general population,[5,6] emphasising the critical need for early screening and identification of affected individuals and their family members.

This paper will review the clinical features, screening and diagnosis of FH, the role of genetic testing, and the treatment options currently available for patients with FH in Singapore.

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GENETICS OF FAMILIAL HYPERCHOLESTEROLAEMIA

FH is an autosomal dominant monogenic disorder with a penetrance of over 90 percent.[7] Individuals with a single copy of an affected allele (heterozygous) will develop clinical phenotype. Heterozygous individuals (HeFH) have clinical manifestations that are less severe when compared to those with two copies of an affected allele (homozygous or HoFH). In individuals with HeFH, 50 percent of offspring will inherit the disorder, while in individuals with HoFH, all offspring will be affected.

The causative genetic mutations occur in three main genes: LDL receptor (LDLR), Apolipoprotein B (ApoB), and Proprotein convertase subtilisin Kexin type 9 (PCSK9). The most common mutation is in the LDLR gene, where more than 2,000 FH-causing mutations have been identified.[8] LDLR mutations accounted for about 90 percent of all mutations identified in a single centre study in Singapore.[9]

LDLR mutations result in reduced numbers or impaired function of LDLR, leading to reduced hepatic clearance and accumulation of LDL-C in plasma.[10] ApoB is a ligand for LDL particle to bind to the LDLR. Loss of function mutations in ApoB therefore results in impairment of LDL-C clearance due to impaired binding to the LDLR.[10,11] PCSK9 is produced mainly in hepatocytes and its role is in intracellular degradation of the LDLR, resulting in a reduced number of LDLR being recycled to the surface of hepatocytes.[12] Individuals with gain of function mutations in PCSK9 gene have a reduced number of LDLR, resulting in impaired LDL-C clearance.

CLINICAL CHARACTERISTICS AND CARDIOVASCULAR RISK IN INDIVIDUALS WITH FAMILIAL HYPERCHOLESTEROLAEMIA

Individuals with HoFH present with a severe clinical phenotype, usually in the first decade of life with physical findings of cholesterol deposition such as tendon xanthomas, corneal arcus, or xanthelasma. LDL-C is usually markedly elevated: untreated LDL-C >10 mmol/L (>400 mg/dL) or treated LDL-C ≥8 mmol/L (≥300 mg/dL).[13] ASCVD develops before the age of 20 years if untreated.[13] Aortic stenosis due to supravalvular cholesterol deposition may also develop, which can lead to left ventricular failure.[13,14]

Individuals with HeFH have LDL-C that is not as high as in HoFH (untreated LDL-C >4.9 mmol/L) and most do not have physical findings at presentation, especially when LDL-C is below 7 mmol/l.[15,16] HeFH is usually diagnosed later in life, around the 4th or 5th decade onwards, with one-third already with ASCVD.[17]

DIAGNOSIS AND GENETIC TESTING IN FAMILIAL HYPERCHOLESTEROLAEMIA

Familial Hypercholesterolemia should be considered in any adult with LDL-C >4.9 mmol/L or with premature ASCVD, defined as age <55 years in men and <60 years in women.[15,18]

FH can be diagnosed using clinical criteria or through genetic testing. The most used clinical criteria are the Dutch Lipid Clinic Network criteria (DLCN) and the Simon Broome criteria.[5] Both criteria include clinical features including LDL-C levels, family history of hypercholesterolemia or early ASCVD, and physical examination findings such as tendon xanthoma. DLCN assigns points for a personal history of premature ASCVD. Both criteria include weightage for a causative genetic mutation. Based on the presence of these features, both the DLCN and Simon Broome criteria assign an individual to be "Definite" or "Possible" FH, while DLCN has an additional intermediate category of "Probable FH".

Genetic Testing

Genetic testing is the definitive method to diagnose FH, considered the gold standard.[19,20] The main benefits of genetic testing include:

1. Availability of a definitive diagnosis of FH
2. Cardiovascular risk prognostication. In those with LDL-C >4.9 mmol/L and presence of a mutation in one of the three causative FH genes had a 22-fold increased CAD risk when compared to the reference group with LDL-C <3.4 mmol/L and no mutation,[21] highlighting the need for urgent, intensive LDL-C lowering in FH.[20]
3. Facilitate cascade screening of first-degree relatives (FDR) of individuals with a positive mutation allowing for early diagnosis.

Genetic testing has been recommended to be part of standard care in FH, especially in individuals who are diagnosed clinically with Definite or Probable FH.[20,22] In Singapore, while genetic testing for FH is currently not routinely available, there is ongoing research exploring the benefits of genetic testing and cascade screening as part of care in FH.[9,23]

The results from genetic testing for FH are classified as either "positive" or "negative". A "positive" result indicates the detection of either a "pathogenic or likely pathogenic variant" in the disease-causing genes for FH. A "negative" result would be when no variant is detected, or when the variant detected is classified as "benign". In some instances, a report might indicate that a "variant of uncertain significance" or "VUS" was detected. As its name suggests, this refers to a situation in which it is uncertain whether this variant has any health impact on FH. In due course, with further studies, this variant may be re-classified as "benign", "pathogenic", "likely pathogenic", or remain as "VUS". Thus the presence of VUS does not exclude FH.

Cascade screening is the most cost-effective strategy for the detection of new asymptomatic patients with FH to reduce ASCVD risk.[20,24,25] Once an individual is diagnosed with FH through genetic testing, FDR are screened for the identified causative genetic mutation. Second- and third-degree relatives are prompted for genetic testing if a genetic mutation is identified in the FDR.[15] Compared to using lipid levels alone, genetic testing is the preferred method for cascade screening as it allows for definitive identification of relatives with and without a causative mutation.[26]

CLINICAL ASSESSMENT OF PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIA

History and examination should include:

1. Presence of symptoms of ASCVD (e.g., exertional angina)
2. Family history of severe hypercholesterolaemia or premature ASCVD
3. Past history of ASCVD
4. Medications
5. Lifestyle habits of smoking, alcohol intake, diet, and exercise
6. Examination for tendon xanthoma, corneal arcus, xanthelasma, and thickened Archilles tendon, which are signs of accumulation due to greater level of cholesterol exposure over an extended period of time[27]

A complete lipid profile, including total cholesterol, triglyceride, HDL-cholesterol, and LDL-C should be obtained. Most patients with FH will have desirable triglyceride and HDL-cholesterol levels.[28] Hypertriglyceridemia and/or low HDL-cholesterol is suggestive of dyslipidaemia associated with metabolic syndrome.[29] As these conditions may co-exist, the presence of hypertriglyceridemia does not exclude FH.[30]

Secondary causes of hypercholesterolaemia like hypothyroidism, obstructive liver disease, and nephrotic syndrome should be excluded.

CARDIOVASCULAR RISK ASSESSMENT IN INDIVIDUALS WITH FAMILIAL HYPERCHOLESTEROLAEMIA

While FH is associated with elevated ASCVD risk, this risk among individuals with FH is heterogenous.[18] ASCVD in FH may be accentuated by other cardiovascular risk factors such as age, diabetes mellitus, hypertension, chronic kidney disease, smoking, and obesity.[31]

Stratification may help to identify individuals with FH who are at exceptionally high risk for ASCVD, necessitating more urgent and aggressive lipid-lowering therapy.[19] Traditional risk calculators such as the Framingham risk score should not be used in FH patients as these underestimate the

cardiovascular risk in FH.[19] Specific risk calculators for FH have been developed[31,32] but are not widely used as they require further validation in different populations.[19]

Lipoprotein(a) or Lp(a) is a lipoprotein that is bound to apolipoprotein(a) and is considered a variant of LDL-C.[18,33] Lp(a) levels are primarily genetically determined, and remain largely consistent throughout life.[33,34] Lp(a) is a causal, independent risk factor for ASCVD.[33] A proportion (30-50 percent) of patients with FH have elevated Lp(a) levels.[35] Individuals with both FH and elevated Lp(a) have a fourfold higher ASCVD risk when compared with individuals with neither condition and a twofold higher when compared with individuals with FH without elevated Lp(a).[36] Measurement of Lp(a) is recommended at least once in a patient's lifetime for risk stratification.[18,36] Despite the unproven clinical benefit of lowering Lp(a) currently,[33,37] the presence of elevated Lp(a) helps in risk stratification and identification of appropriate LDL-C targets and intensive management of reversible cardiovascular risk factors in those with elevated Lp(a), especially when co-existing with FH.

MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLAEMIA

Individuals with FH have a lifelong, cumulative elevation in LDL-C with increased risk of premature ASCVD.[13] Early intervention to reduce LDL-C in FH reduces the risk of ASCVD and mortality to near that of the general population.[6,38] The benefit on cardiovascular mortality is especially observed in patients without ASCVD, further underscoring the importance of early identification and treatment.[38]

LDL-C Targets

LDL-C is the primary target of therapy for prevention of ASCVD.[39] The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines recommend an initial 50 percent reduction from baseline in LDL-C, followed by achievement of target LDL cholesterol according to a patient's risk: <1.8 mmol/L for individuals with FH and no ASCVD, and <1.4 mmol/L for individuals with FH and ASCVD.[40]

Evidence for these lipid targets were from 1) meta-analysis showing ASCVD risk reduction commensurate with the degree of LDL lowering; 2) PCSK9 inhibitors trials proving the benefits and safety of LDL-C lowering below 1 mmol/l; and 3) expert opinion.[19,40]

Apart from ESC-EAS guidelines, in those with FH without ASCVD, other experts suggest to further stratify the targets according to presence of additional risk factors, targeting <2.6 mmol/l in those with FH below 40 years of age and without any other ASCVD risk factors, and <1.8 mmol/l for the rest with FH without ASCVD.

To achieve these LDL-C targets and outcomes in FH, lipid-lowering therapy should be initiated at diagnosis of FH for adults[22] for children from age 8-10 years.[22]

Statins

Statins are first-line lipid lowering therapy due to extensive evidence showing its efficacy in reducing LDL cholesterol, cardiovascular events, and mortality in both FH and non-FH patients.[6,38,41] Statins work by reducing hepatic cholesterol production through inhibition of the enzyme HMG-CoA reductase. This results in a drop in intracellular cholesterol, promoting an increase in number of LDLR on the cell surface of hepatocytes, enhancing LDL-C uptake into the cell, and reduced plasma concentration of LDL-C.[40]

Response to statin treatment is variable in FH, dependent on the severity of the mutation and residual LDL receptor function.[42] Current guidelines recommend initiating maximally tolerated high-potency statins (Atorvastatin, Rosuvastatin) for patients with FH.[19,22] High potency statins are recommended in order to achieve the 50 percent LDL-C reduction.[22,40]

Statin-associated muscle symptoms (SAMS) occur in 7-29 percent of patients on statin treatment.[43] For patients who develop SAMS, reversible causes such as hypothyroidism and vitamin D deficiency should be excluded. Statin therapy may be stopped for 2-4 weeks and then restarted using an alternate statin, or using the same statin with alternate day or once/twice weekly dosing.[43]

Most patients with FH will be not reach their LDL-C goal with statin therapy alone and second-line therapies (Ezetimibe or PCSK9 inhibitors) are required.[44]

Ezetimibe

Ezetimibe is a selective cholesterol absorption inhibitor and works by blocking the NPC1L1 transporter on the intestinal epithelium.[45] Ezetimibe leads to an additional 20 percent reduction in LDL-C when added to statins and is well tolerated.[40,46.] The IMPROVE-IT, which was a randomised control trial conducted in 18,144 patients who were recently hospitalised for acute coronary syndrome, showed that the addition of ezetimibe to simvastatin led to an estimated 10 percent reduction in cardiovascular events.[47] IMPROVE-IT was not conducted specifically in FH patients, although other smaller RCTs have shown efficacy in LDL-C lowering for patients with FH.[46]

PCSK9-based Therapies

PCSK9 inhibitors are a class of injectable lipid-lowering medications, first available in Singapore since 2017. They are monoclonal antibodies that inhibit PCSK9 action, resulting in diminished intracellular degradation of the LDL-receptor and more LDLR on the cell surface.[48]

In FH, PCSK9 inhibitors are recommended as a third-line treatment, if LDL-C targets are not achieved with maximally tolerated doses of statins and ezetimibe.[19] In clinical trials, PCSK9 inhibitors have shown an additional 50-70 percent reduction in LDL-C when added to statins and ezetimibe, in both FH and non-FH patients.[49,50,51] PCSK9 inhibitors have also shown improved cardiovascular outcomes in

patients with established cardiovascular disease.[49,50] The utility of PCSK9 inhibitors has been limited by its high cost,[52] although it has been considered cost-effective when used in FH.[53] In Singapore, cost subsidies have recently been introduced.[54]

A more recent PCSK9-based therapy is Inclisiran, a small interfering RNA that blocks hepatic synthesis of PCSK9. When compared to PCSK9 inhibitors, Inclisiran is equally effective in lowering LDL-C in FH and is administered subcutaneously every six months.[55]

Diet and Lifestyle Management

Dietary management should be implemented for all individuals with FH.[22] A diet lower in saturated and trans-fat, and higher in polyunsaturated fat and plant sterol intake, should be advised.[56] Dietary intervention in FH has shown only modest lowering of LDL-C (~5-10 percent) in FH.[57] In most patients, LDL-C goals cannot be achieved with dietary changes alone, therefore the recommendation to start statins at the point of diagnosis.[19,22,56]

Apart from dietary management, individuals with FH should be advised on other healthy lifestyle choices, including regular exercise, stopping smoking, reducing alcohol intake and weight loss if overweight. Co-morbidities such as hypertension and Diabetes Mellitus should be screened and managed.

Homozygous FH

HoFH requires aggressive lipid-lowering treatment due to the risk of high mortality if untreated.[58] Treatment of HoFH is often requires a multi-drug regime to lower LDL cholesterol. Statins are often not as effective due to a loss of function of LDLR.[13] Lipid apheresis every 1-2 weeks has been shown to lower LDL cholesterol adequately.[40] PCSK9-based therapy and other novel therapies including mipomerson, lomitapide, and ANGPTL3 inhibitors have been used in HoFH.

CONCLUSION

Familial Hypercholesterolemia is a common genetic disorder associated with high cardiovascular risk that can be attenuated with early detection and intervention. Cascade screening is key in early identification of individuals affected by this disorder.

Most individuals with FH will require multiple lipid-lowering medications in order to achieve LDL-C goals.

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LEARNING POINTS

- **FH is a common genetic disorder, caused by mutations in LDL receptor, Apolipoprotein B, or PCSK9 and is characterised by elevated LDL cholesterol and premature cardiovascular disease. HoFH usually presents in childhood with physical signs of cholesterol deposition, while HeFH is often "silent", under-diagnosed or diagnosed only later in adulthood through routine screening or after the onset cardiovascular disease.**
- **Early diagnosis and treatment of hypercholesterolaemia in FH is critical to reduce cardiovascular events and mortality.**
- **FH can be diagnosed through clinical criteria or genetic testing. Genetic testing provides a definitive diagnosis of FH, informs cardiovascular prognostication, and facilitates cascade screening of family members.**
- **Cascade screening of family members of affected individuals is the most cost-effective method to identify new individuals with FH.**
- **Statins should be initiated at diagnosis of FH in order to achieve an adequate reduction in LDL-cholesterol. Most individuals with FH will require the addition of Ezetimibe and PCSK9 inhibitors to achieve LDL targets. Dietary management alone is inadequate in FH.**