Chapter

Familial Hypercholesterolemia

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Abstract

Familial hypercholesterolemia is a genetic and metabolic disorder associated with an increased risk of morbidity and mortality. Two main types of familial hypercholesterolemia are distinguished: heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia. Homozygous familial hypercholesterolemia progresses much more aggressively with higher levels of LDL-C and higher risk of cardiovascular disease at earlier ages. The prognosis of homozygous familial hypercholesterolemia largely depends on the LDL-C levels. Reducing the LDL-C level is one of the primary goals of treatment patients with familial hypercholesterolemia. Effective control of LDL-C significantly reduces the cardiovascular morbidity and mortality. Understanding the factors likely to affect treatment adherence is paramount. Adherence to treatment can be improve when a genetic etiology is confirmed. Positive genetic test result has beneficial effects on adherence to pharmacotherapy and in achieving LDL-C levels reduction.

Keywords: familial hypercholesterolemia, adherence, illness perception, barriers, diagnose

1. Introduction

This chapter reviews the definition, etiology, course and treatment of familial hypercholesterolemia, and analyses the influence of some factors that may influence the early diagnosis of familial hypercholesterolemia and the treatment of familial hypercholesterolemia.

2. Definition and etiology of familial hypercholesterolemia

Familial hypercholesterolemia (FH) is a genetic and metabolic disorder that affects the metabolism of cholesterol [1–10].

Currently, the genes involved in HF are the following: low-density lipoprotein receptor (LDLR) gene, apolipoprotein B-100 (APOB) gene and proprotein convertase subtilisin kexin type 9 (PCSK9) gene, LDLR adaptor protein 1 (LDLRAP1) gene [1–10]. See **Table 1**.

The mutation in LDLR gene, APOB gene and PCSK9 gene is inherited following an autosomal dominant/autosomal co-dominant pattern and the mutation in LDLRAP1 gene is inherited following an autosomal recessive pattern [1–10].

Mutations of the genes cause defective LDL uptake and degradation, which in-turn leads to an elevation of plasma low-density lipoprotein-cholesterol (LDL-C) level, producing the hypercholesterolemia phenotype. The chronic exposure to high levels of LDL-C lead to the development of atherosclerosis and cardiovascular disease at an early age [1–10].

Gene	Protein	Chromosomal location	Proportion of patients with FH
LDLR	LDL receptor	19p13.2	80–85%
APOB	Apolipoprotein B100	2p24.1	5–10%
PCSK9	Proprotein convertase subtilisin kexin type 9	1p32.3	< 1%
LDLRAP1	LDL receptor adaptor protein 1	1p36.11	< 1%

Table 1.
Genes involved in familial hypercholesterolemia.

Two main types of HF are distinguished: heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia. Heterozygous familial hypercholesterolemia is usually caused by a single pathogenic variant in one of the genes associated with familial hypercholesterolemia, mostly in LDLR. Homozygous familial hypercholesterolemia is caused by biallelic pathogenic variants, generally in LDLR [1–10].

3. Diagnosis of familial hypercholesterolemia

Familial hypercholesterolemia often diagnosed using the following diagnostic criteria: UK Simon Broome System and the Dutch Lipid Clinic Network criteria [11–17].

The UK Simon Broome System Criteria can be applied in children/adolescents/adults. The items included in Simon Broome System are the following: laboratory findings (total cholesterol or LDL-C), physical examination (tendon xanthomas), molecular diagnosis (mutation LDLR, APOB or PCSK9), and family history (myocardial infarction, raised total cholesterol) [11–17]. UK Simon Broome System Criteria is attached in **Table 2.**

Items	Criterion
In adults (age ≥ 16): total cholesterol level > 290 mg/dL	A
or LDL-C > 190 mg/dL	
In children (age < 16): total cholesterol level > 260 mg/dL	B
or LDL-C > 155 mg/dL	
Tendon xanthomas in the patient or in a first- or	
second-degree relative	
DNA-based evidence of a mutation in LDLR, APOB, or	C
PCSK9	
Family history of myocardial infarction before age 50	D
in a second-degree relative, or before age 60 in a first degree	
relative	
Total cholesterol >290 mg/dL in a first- or second degree	E
relative	
C or A plus B: Definite familial hypercholesterolemia	
A plus D or A plus E: Probable familial hypercholesterolemia	

Table 2.
UK Simon Broome system criteria.

The Dutch Lipid Clinic Network Criteria can be applied in adults. The items included in Dutch Lipid Clinic Network are the following: laboratory findings (LDL- C), physical examination (tendon xanthomas, arcus cornealis), molecular diagnosis (mutation LDLR, APOB or PCSK9), family history (atherosclerotic cardiovascular disease, tendon xanthomas, arcus cornealis, raised LDL- C), and patient history (coronary artery disease, cerebral or peripheral vascular disease) [11–17]. Dutch Lipid Clinic Network Criteria is attached in **Table 3.**

The diagnostic criteria mentioned differ in the items included and, in the items necessary to make a definitive FH diagnosis. In the Simon Broome criteria, a positive genetic test is sufficient for a definitive diagnosis of familial hypercholesterolemia. In the Dutch Lipid Clinic Network criteria, a positive genetic test should be accompanied by an additional item (for example, elevated LDL-C levels) to fulfill the definite diagnosis criteria [11–17].

Although all the criteria mentioned include LDL- C levels, there are variations in the cut-offs necessary for the diagnosis of familial hypercholesterolemia. It is worth mentioning that untreated LDL-C levels vary across genotypes. For example: levels are highest with two LDLR null alleles, lower with two LDLR defective alleles or two mutant PCSK9 alleles, and lowest with two mutant APOB alleles and in double heterozygotes [18–26].

Regardless of the diagnostic criterion used, before the diagnosis of familial hypercholesterolemia is confirmed, secondary causes of hypercholesterolemia should be excluded such as hypothyroidism, renal disease, nephrotic syndrome, liver disease and diets with extremely elevated saturated fat/cholesterol content.

Items	**Score**
First-degree relative with known premature atherosclerotic cardiovascular disease (age < 55 in men, age < 60 in women) or first-degree relative with LDL-C > 95th percentile	1
First-degree relative with tendon xanthomas or arcus cornealis, or child (under age 18) with LDL-C > 95th percentile	2
Premature coronary artery disease	2
Premature cerebral or peripheral vascular disease	1
Tendon xanthomas	6
Arcus cornealis before age 45	4
LDL-C ≥ 330 mg/dL	8
LDL-C between 250 and 329 mg/dL	5
LDL-C between 190 and 249 mg/dL	3
LDL-C between 155 and 189 mg/dL	1
Functional mutation in the LDLR, APOB, or PCSK9 gene	8
Score > 8 Definite familial hypercholesterolemia	
Score between 6 and 8 Probable familial hypercholesterolemia	
Score between 3 and 5 Possible familial hypercholesterolemia	
Score < 3 Unlikely	

Table 3.
Dutch lipid clinic network criteria.

Furthermore, there are several conditions with overlapping laboratory findings or family history features that might be considered when a diagnosed of familial hypercholesterolemia is suspected. For example: sitosterolaemia (xanthomas and hypercholesterolemia caused by an autosomal recessive pathogenic variant in ABCG5 or ABCG8) and lysosomal acid lipase deficiency (elevated LDL-C levels accompanied by fatty liver disease could be caused by an autosomal recessive pathogenic variant in LIPA) [27–29].

Once an individual is identified with familial hypercholesterolemia (index case) the cascade screening of family members of the known index case is recommend for identify new cases of familial hypercholesterolemia. Cascade screening could include LDL-C measurement, genetic testing, or both [11–17, 30].

Though the diagnosis of familial hypercholesterolemia can be performed without genetic testing (for example, using Simon Broome criteria), when a mutation compatible with familial hypercholesterolemia is identified, genetic testing serves to confirm the diagnosis of FH. Furthermore, genetic testing could provide discrimination, at the molecular genetic level, between homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia. Moreover, pre-test and post-test genetic counseling can facilitate patient's interpretation of genetic test results [11–17].

The International Classification of Diseases, 10th Revision, has a specific diagnose criteria for homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia (E78.01) [31].

The ICD10 criteria for heterozygous familial hypercholesterolemia are the following: LDL-C ≥ 160 mg/dL (4 mmol/L) for children or LDL-C ≥ 190 mg/dL (5 mmol/L) for adults and: a first-degree relative who is similarly affected or a first-degree relative with positive genetic testing for an LDL cholesterol-raising defect in LDLR, APOB or PCSK9 [31].

The ICD10 criteria for Homozygous familial hypercholesterolemia are the following: LDL-C ≥ 400 mg/dL (10 mmol/L) and: one or both parents with clinically diagnosed familial hypercholesterolemia or one or both parents with positive genetic testing for two identical (homozygous familial hypercholesterolemia) or non-identical (compound or double heterozygous familial hypercholesterolemia) LDL cholesterol-raising gene defects in LDLR, APOB or PCSK9 or one or both parents with autosomal recessive familial hypercholesterolemia [31].

Familial hypercholesterolemia is considered underdiagnosed. During the diagnosis process, some barriers might arise to early diagnosis of familial hypercholesterolemia in patients and relatives. From medical point, for example: physician's knowledge of FH diagnoses and treatment, the lack of a uniform clinical criteria for FH diagnosis, the availability of genetic testing, physician's knowledge about screening methods (selective, opportunistic, universal, cascade) and the identification of probable cases in different health care levels. From patient point, for example: some patients do not want a personal diagnosis to be disclosed to relatives, some parents experience feelings of guilt related to passing their mutation to their children, and many patients interpret their negative genetic test result as meaning their do not have FH hypercholesterolemia or that their FH hypercholesterolemia is not genetic and thus their relatives cannot have FH [1, 32].

Machine learning and deep learning approach could enhance the identification of familial hypercholesterolemia patients using electronic health record data. For example: the FIND FH model. This model recognizes the clinical phenotype for familial hypercholesterolemia and provides the framework for a HIPAA-compliant method to contact these identified individuals with FH [33–36].

4. Course disease and treatment of familial hypercholesterolemia

The signs and symptoms of homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia are similar. However, homozygous FH patients have higher levels of LDL-C and higher risk of cardiovascular disease. The disease progresses much more aggressively, the phenotype become clinical manifest earlier, and cardiovascular events occur at earlier ages in homozygous FH patients. Cardiovascular risk factors and lipoprotein(a) levels adversely affect the course of homozygous and heterozygous FH diseases increasing coronary heart disease rates [11–12, 14–16, 37–43].

The prognosis of homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia largely depends on the LDL-C levels. Reducing the LDL-C level is one of the primary goals of treatment homozygous and heterozygous FH. Effective control of LDL-C significantly reduces the cardiovascular morbidity and mortality. To improve cardiovascular risk assessment, the use of imaging techniques to detect asymptomatic atherosclerosis is recommended in both homozygous and heterozygous FH [11–12, 14–16, 41–43].

The carotid intima-media thickness is greater and aortic lesions can be seen identified in heterozygous FH patients between 8 to 10 years of age. During adolescence about 25% of the adolescents with heterozygous FH have demonstrable coronary artery calcium. Clinical manifestation of coronary heart disease can be evident in heterozygous FH patients during the third decade of life. Physical manifestations of sustained elevations of LDL-C (tendon xanthomas and corneal arcus) become apparent during adulthood [44–49].

At birth, homozygous familial hypercholesterolemia patients have a $\geq$ 4-fold increase in plasma LDL-C concentrations. Since early in life cholesterol deposits in tendons (xanthomas), in the cornea (corneal arcus) and around the eye (xanthelasma). Furthermore, cholesterol deposits in coronary arteries, carotid arteries, aortic root, and valve. Therefore, coronary heart disease and supravalvular and aortic valve stenosis are possible causes of death. Young adults with homozygous familial hypercholesterolemia often require aortic valve replacement. Non-invasive imaging can be used to monitor atherosclerotic and aortic valve disease progression in homozygous FH patients and to adjusted treatment [50–55].

Treatment of FH is long-term and involves pharmacotherapy, lifestyle modifications and control other cardiovascular risk factors such as hypertension, diabetes, tobacco smoking, obesity, and sedentary behavior [12, 14–16, 41–42, 56–61].

Statins are the mainstay pharmacotherapy. However, if maximal tolerated dose of statin is used and LDL-C goal not achieved, statins usually combined with ezetimibe. Additionally, if using statin-ezetimibe combination LDL-C goal not achieved, adding PCSK9 inhibitors is considered [12, 14–16, 41–42, 56–65]. The European Atherosclerosis Society/European Society of Cardiology plasma low-density lipoprotein-cholesterol goals [57] for patients with familial hypercholesterolemia are summarized in **Table 4**.

Patients with PCSK9 mutations are particularly responsive to PCSK9 inhibition. However, PCSK9 inhibitors had no effect on LDL cholesterol in those with two LDLR null alleles with homozygous familial hypercholesterolemia. Moreover, if at least one allele had residual LDLR activity, PCSK9 inhibitors lowered LDL cholesterol in patients with homozygous familial hypercholesterolemia [66–69].

Incomplete/low adherence to treatment is associated with increased risk of cardiovascular disease. A proportion of FH patients fall short of full compliance or follow regimens inconsistently. Understanding the factors likely to affect treatment adherence is paramount [70–79].

The European Atherosclerosis Society/European Society of Cardiology (2019) recommends the following goals for plasma low-density lipoprotein-cholesterol for patients with familial hypercholesterolemia:
LDL-C < 3.5 mmol/L in children
LDL-C < 1.8 mmol/L and a reduction in plasma LDL-C of >50% in subjects without other major risk factors (high risk)
LDL <1.4 mmol/L and a reduction in plasma LDL-C > 50% in subjects with one or more major cardiovascular disease (CVD) risk factors and/or existing CVD (very high risk)

Table 4.
LDL-C goals for patients with familial hypercholesterolemia.

As well as in other chronic pathologies that require long-term treatment, psychological and cognitive issues can influence adherence to treatment [70–79].

While there is no evidence of depression or anxiety in FH patients, instead there is evidence of cognitive deficits and mild cognitive impairment in FH patients. Deficits in executive functioning and memory may affect medication adherence because taking medicines involves developing and implementing a plan to adhere and remembering the plan (for example: the plan may require time-based (e.g., at 8:00 p.m.) or event-based prospective remembering (e.g., with meals) and remembering what medicine take and whether the medicine was taken). Furthermore, executive functions may affect the achievement of lifestyle modifications and maintain healthy behavior over time included in FH management [70–76].

Ilness perceptions may affect adherence to both lifestyle interventions and medications. Perception of illness/perception of risk may affect FH patient behavior. Risk perception may be changed by personal or familiar events, such as a cardiovascular event in the family, a change in or an onset of symptoms and becoming parent. Health staff need to recognize variation in patient's risk perception because it can affect medical treatment [77–79].

Adherence to FH treatment can be improve when a genetic etiology is confirmed. Positive genetic test result has beneficial effects on adherence to pharmacotherapy and in achieving LDL-C levels reduction. Patients whose diagnosis was confirmed by genetic testing perceived diagnosis more accurate, believed more strongly that genes controlled their cholesterol and have higher perceived efficacy of medication. In children with FH, parents are critical in promoting treatment adherence [77, 80–85].

5. Conclusions

Although the diagnosis of familial hypercholesterolemia can be performed without genetic testing, knowledge about the genetic status of an individual with familial hypercholesterolemia can improve understand of risk and prognosis as well as improve managing familial hypercholesterolemia. Adherence to FH treatment can be improve when a genetic etiology is confirmed.

Conflict of interest

The authors declare no conflict of interest.

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