FAMILIAL HYPERCHOLESTEROLEMIA AND CASCADE SCREENING FOR DETECTION OF NEW PATIENTS

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Abstract

Familial Hypercholesterolemia (FH) is a metabolic disorder that is inherited in an autosomal dominant manner and is characterized by elevated cholesterol levels and the development of premature atherosclerotic cardiovascular disease (ASCVD). The prevalence of heterozygous FH is 1 in 250-500 individuals, while the prevalence of homozygous FH is 1 in a million. The molecular basis of this condition involves mutations in the genes encoding the LDL receptor (Low-Density Lipoprotein Receptor, LDLR), Apolipoprotein B (ApoB), or Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) enzyme. In patients with FH, laboratory analyses are dominated by elevated levels of low-density lipoprotein cholesterol (LDL-C) above the 95th percentile for age and gender, with most commonly normal values of high-density lipoprotein cholesterol (HDL-C) in very low-density lipoprotein cholesterol (VLDL-C), and triglycerides. The gold standard for diagnosing FH is genetic analysis and mutation detection, but it is often inaccessible due to economic reasons. Today, the diagnosis is made by applying a scoring system within well-validated questionnaires, which assess the probability of FH based on the simultaneous analysis of personal and family history, clinical findings of tendon xanthomas or corneal arcus, as well as biochemical analysis of the lipid profile. Despite clear diagnostic recommendations for FH, there is an extremely low rate of diagnosis of these patients, even in developed healthcare systems, as well as a low rate of treatment. A large number of unrecognized FH patients, along with a significantly increased risk of cardiovascular diseases in untreated young FH patients, have prompted global efforts to diagnose the disease earlier and reduce complications through appropriate treatment. Cascade screening in the detection of new patients involves analyzing the relatives, first-, second-, and third-degree, of patients with known FH (index case, *proband*). Upon identifying a new case, that individual becomes the new *proband*, and their relatives are analyzed in subsequent cascades. There are three basic models of cascade screening: clinical, genetic, and hybrid models. Currently, selective clinical cascade screening is most commonly applied. Selective cascade screening detects the disease in individuals at high risk of its manifestation. The expert consensus panel recommends a hybrid model, where genetic testing is performed in all patients with definite or probable FH, and in cascade screening, both cholesterol levels and genetic analysis are continued in their high-risk relatives. Adequate detection of FH patients and timely treatment significantly reduce their cardiovascular morbidity and mortality, justifying the implementation of cascade screening. Conducting screening through routine clinical practice does not yield satisfactory results. Therefore, it is necessary to organize a screening program at the national level, including the establishment of lipidology centers and the provision of genetic screening and genetic counseling services.

Keywords: Familial hypercholesterolemia, dyslipidemia, cascade screening, genetic testing, primary prevention

Introduction

Familial hypercholesterolemia (FH) is a metabolic disorder that is inherited in an autosomal dominant manner and is characterized by elevated cholesterol levels and the development of premature atherosclerotic cardiovascular disease (ASCVD). Long-term exposure to high levels of LDL-C throughout life increases the risk of cardiovascular diseases (CVD) in these patients by 10 to 20 times[1]. The prevalence of heterozygous FH is 1 in 250-500 individuals, making it the most common genetic disease with significant clinical manifestations. The prevalence of homozygous FH is 1 in a million[2].

The molecular basis of this autosomal dominant disorder involves mutations in the genes for the LDL receptor (LDLR), apolipoprotein B (ApoB), or PCSK9 enzyme. Mutations in the LDLR gene account for 85 to 90% of FH cases[3]. Mutations in the ApoB gene are responsible for approximately 5 to 10% of FH cases in patients from northern Europe. Elevated levels of Lp(a) have a genetic basis within the context of FH but are influenced by polygenic mutations[4].

In patients with FH, laboratory analyses typically show elevated levels of LDL-C (above the 95th percentile for age and gender), while HDL-C, VLDL, and triglyceride levels are usually within normal ranges. In heterozygotes, total cholesterol usually elevates from 7.5-13 mmol/L, and in LDL-C elevates from 5.1-10.3 mmol/L. Elevated levels of cholesterol in early childhood are significant diagnostic markers. Lp(a) is often elevated as well. The presence of tendon xanthomas and xanthelasmas is pathognomonic in clinical findings[5].

According to the recommendations of the European Atherosclerosis Society (EAS), suspicion of FH arises when total cholesterol is > 8 mmol/L in adult individuals, or LDL-C is > 5 mmol/L in adults or > 4 mmol/L in children, in the presence of tendon xanthomas in the individual or a family member, premature atherosclerosis in the individual/family member, or sudden cardiac death in a family member. It is important to refer patients with suspected FH to a specialized lipidology center[1].

The gold standard for diagnosing FH is the detection of genetic mutations through genetic analysis, but it is often unavailable due to economic reasons. Currently, the diagnosis is made using scoring systems within well-validated questionnaires. These questionnaires assess the probability of FH based on the simultaneous analysis of personal and family history, clinical findings, and biochemical analysis of lipid profiles. The diagnostic criteria of the Dutch Lipid Clinic Network (DLCN) are applied at the University Clinical Center of Serbia (table 1)[6]. In addition to the DLCN criteria, the Simon Broome[7] criteria and MEDPED (Making Early Diagnosis to Prevent Early Death) criteria are also used (table 2)[8].

However, despite clear guidelines for the diagnosis of FH, there is a significantly low rate of diagnosis for these patients, even in developed healthcare systems. It is estimated that there are 1.3 million individuals with FH in the United States, yet less than 10% have been diagnosed[9]. In a study analyzing data from 180 countries, it was shown that FH is diagnosed in less than 1% of cases in most countries, except for the Netherlands where the diagnosis rate was 76%, and Norway at 43%[10]. Another significant problem is the

Table 1. Dutch Lipid Clinic Network criteria for the diagnosis of heterozygous FH

	CRITERIA	SCORE
Family history:	a) premature* coronary and/or vascular disease	1
	b) LDL-C values > 95th percentile for age and gender:	
	1) in an adult relative	1
	2) in a relative younger than 18 of age	2
	c) xanthoma or *arcus cornealis*	2
Personal history: The patient has a history of premature*	a) coronary artery disease	2
	b) cerebral or peripheral vascular disease	1
Physical examination of the patient:	a) presence of xanthomas	6
	b) *arcus cornealis* in a patient younger than 45 of age	4
LDL-C value of the patient (mmol/L)	a) ≥ 8.5	8
	b) 6.5 - 8.4	5
	c) 5.0 - 6.4	3
	d) 4.0 - 4.9	1
DNA analysis:	Presence of mutations in LDL receptor or other FH-relevant genes	8
Diagnosis:		Point score
	Definite FH	≥ 8.5
	Probable FH	6-7
	Possible FH	3-5

Adapted from: *Fouchier SW, Defesche JC, Umans-Eckenhausen MW, Kastelein JP. The molecular basis of familial hypercholesterolemia in The Netherlands. Hum Genet. 2001 Dec;109(6):602-15*

Table 2. USA MEDPED - Total cholesterol and LDL-C cut-off values for diagnosis FH among relatives of an index case with FH

Age (years)	TOTAL CHOLESTEROL AND LDL-C (bracket) mmol/L RELATIVES		
	First degree *	Second degree **	Third degree ***
< 18	5.2 (4.0)	5.9 (4.3)	6.2 (4.4)
18-29	6.2 (4.4)	6.5 (4.6)	6.7 (4.8)
30-39	7.0 (4.9)	7.2 (5.2)	7.5 (5.4)
≥ 40	7.5 (5.3)	7.8 (5.6)	8.0 (5.8)

Legend: * parents, children, siblings; ** grandfather, grandmother, grandchildren, aunts, uncles, nieces, nephews, step brothers and step sisters; *** great-grandmother, great-grandfather, great-grandchildren, other cousins
Adapted from: *Williams RR, Hunt SC, Schumacher MC, Hegele RA, Leppert MF, Ludwig EH, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol. 1993 Jul 15;72(2):171-6*

inadequate treatment of these patients. According to the results of a large Danish population study, the prevalence of cardiovascular disease (CVD) among their subjects with definite or probable FH was 33%, but only 48% of patients were receiving statin therapy[11].

A large number of unrecognized FH patients and the significantly increased risk of developing cardiovascular diseases in young untreated FH patients have driven global efforts to diagnose the disease earlier and reduce complications through appropriate treatment, as well as to minimize the treatment costs for these patients[12]. According to the recommendations of the World Health Organization (WHO), FH meets the criteria for implementing cascade screening to identify new patients[13].

Cascade screening

Cascade screening involves analyzing the relatives of a known FH patient (index case, *proband*). Once a new case is identified, they become the new *proband*, and their relatives are analyzed in subsequent cascades. Since FH is inherited in an autosomal dominant manner, the probability of the disease occurring in first-degree relatives is 50%, and in second-degree relatives is 25%[9].

There are multiple models for cascade screening. Through the evaluation of their effectiveness and efficiency in detecting new FH patients, new insights have been gained about FH itself and the complexity of this metabolic disorder. Cascade screening programs differ in terminology, classification, and applied testing. There are three main models of cascade screening: clinical, genetic, and hybrid[14].

The clinical model of cascade screening

According to the recommendations of the European Atherosclerosis Society (EAS) and the European Society of Cardiology (ESC), the clinical cascade screening for FH involves analyzing the lipid status of family members of the FH *proband*[1]. The clinical screening model can be either universal or selective, with selective cascade screening being the most commonly used approach. Selective cascade screening aims to detect the disease in individuals at high risk of developing FH. The foundation of screening is the accurate diagnosis of the index case with FH. After identifying the index case, the cholesterol levels of their children, parents, siblings, and other relatives are determined[13, 14]. The USA MEDPED scoring system is used to diagnose FH based on the cholesterol values of the relatives, as shown in table 2.

In some countries, the universal screening model is implemented. Universal screening involves broader testing within the population, not just within high-risk groups. Several years ago, researchers from Slovenia demonstrated the effectiveness of this screening model. They conducted genetic testing on all children with total cholesterol levels greater than 6 mmol/L or greater than 5 mmol/L with positive family history and found that half of the tested children had detected mutations for FH, with one of their parents having probable FH[15]. The expert committee of the National Lipid Association (NLA) in the United States also recommends universal screening. In this approach, all children aged 9 to 11 years or older than two years with a family history of elevated cholesterol or early ASCVD are tested[16].

Genetic model of cascade screening

Identifying the causal mutation through genetic testing is the gold standard for diagnosing FH. Relatives of the index case need to be tested and the presence of the identified mutation should be analyzed. The probability of detecting new patients with FH is significantly increased through genetic testing in cascade screening. It is important to emphasize that the inability to detect a mutation does not exclude the diagnosis of FH. If the tested relative, in whom the mutation has not been confirmed, has cholesterol levels that require treatment, it is necessary to introduce statins in their therapy[14]. The polygenic mechanism of inheritance is the most common cause of hypercholesterolemia in these patients. Formally, there is no guideline for clinical cascade testing in America, but the significance of genetic testing for FH in detecting new patients is recognized by the Centers for Disease Control and Prevention (CDC), which has recommended FH as one of four diseases for which genetic testing is necessary[17].

The implementation of cascade screening for the early detection and treatment of family members of FH patients has been shown to reduce mortality and morbidity in these patients in several countries. According to data from the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort), the detection of 9,000 new FH cases over 10 years prevented 847 coronary events, including 203 deaths[12, 13]. Cascade testing using a hybrid model has been recommended for identifying new FH cases, and according to the recommendations of the National Institute for Health and Care Excellence (NICE), it has proven to be effective in the implementation in the UK[18, 19]. The effectiveness of cascade screening has also been confirmed through its implementation in the Netherlands, where an average of 8 relatives with FH was identified for each *proband*[20]. Cascade screening is effectively applied in Australia[21] and Brazil[22] as well. A study by Tada et al. demonstrated that cascade screening detects FH in family members 18 years earlier than in *probands* (39 *vs* 57 years) and that the use of even the lowest dose of statins reduces the development of major cardiovascular events by 33% compared to the index case[23].

The hybrid model of cascade screening

Since LDL-C levels in patients with and without FH can overlap, if only clinical testing is performed, 20% of family members who have an LDLR mutation will remain undiagnosed. Therefore, it is necessary to conduct genetic cascade testing It is also important to note that a negative genetic analysis does not exclude the presence of FH. Therefore, it is understandable that the hybrid screening model is considered the only comprehensive model[24]. An expert consensus panel recommends the hybrid model (genetic testing should be done for all patients with definitive or probable FH, and cascade screening should be continued to determine cholesterol levels and genetic analysis in their high-risk relatives)[25]. Understandably, genetic testing requires high financial resources, which is why it is not always possible to apply it, although there are clear recommendations.

Despite clear recommendations for conducting FH screening and the evident effects of its implementation, screening is still not fully carried out in most countries. Amy Peterson and colleagues published the results of a study analyzing the implementation of cascade screening by 500 primary care physicians and 500 cardiologists in the United States, showing that 54% of physicians always conduct screening in adults, while 74% would refer children to a pediatrician for screening. Timely initiation of statin therapy is a much greater problem. Most commonly, they would initiate therapy in patients aged 18 to 27 years, with only 17% recommending statins for boys and just 14% for girls who require statin therapy[26], despite the known recommendations from the Association of pediatricians[27] and the Association of cardiologists[28] that statins can be used from the age of eight. Certain recommendations for the treatment of high cholesterol introduce some confusion in this regard, stating that testing children and initiating therapy is rational, but its effectiveness is not confirmed[29].

Conclusion

FH is a frequent metabolic disorder that, despite clear recommendations for diagnosis and treatment, has a significantly low rate of patient detection and adequate treatment, even in developed healthcare systems. Adequate identification of FH patients and forehand treatment significantly reduce cardiovascular morbidity and mortality, fully justifying the implementation of cascade screening. Conducting screening through daily clinical practice does not provide adequate results. Therefore, it is essential to organize a screening program at the national level, including the establishment of lipidology centres and the possibility of genetic screening and genetic counseling[30].

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