Clinical Lipidology

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Underutilization of cascade screening for familial hypercholesterolemia

"Clinicians attempt to optimally treat their individual patients with elevated cholesterol, especially those with documented coronary heart disease."

Keywords: cascade screening • familial hypercholesterolemia • genetics of coronary heart disease

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Why cascade screening for familial hypercholesterolemia

Cascade screening in the context of dyslipidemia refers to cholesterol testing of close relatives of individuals who fulfill genetic or phenotypic criteria for the diagnosis of familial hypercholesterolemia (FH). One half of first-degree relatives of probands with the disease will be similarly affected, as will a fourth of second-degree relatives. Heterozygous FH occurs in 1 in 300–500 individuals worldwide. It is not a rare genetic disease. It is at least ten-times more common than cystic fibrosis, and is considerably more prevalent than other genetic diseases affecting the cardiovascular system, such as long QT or Marfan syndromes. An LDL cholesterol (LDL-C) level greater than 190 mg/dl, especially when there is a strong history of premature heart disease, strongly correlates with genetically proven heterozygous FH. Untreated, it causes a disproportionate share of the burden of cardiovascular disease, conferring a 20-fold lifetime risk of coronary heart disease (CHD) when compared with the general population [1]. An autosomal codominant disease, FH is caused by molecular defects in the LDL receptor gene (*LDLR*), its protein ligand (*APOB*) or mutations in the *PCSK9* gene. It is generally quite responsive to statin therapy. More recently, *PCKS9* inhibition of protease degradation of diminished LDL receptor function has emerged as an exciting new pharmacologic intervention [2].

It is well documented that atherosclerosis begins during childhood [3]. The process is accelerated when FH is present. Vivid demonstration of the deleterious effect of very high LDL levels on atherosclerotic cardiovascular disease is evident in children who inherit the defective allele from both parents, resulting in homozygous FH. LDL-C levels are typically above 450 mg/dl, and death from cardiovascular disease usually occurs in the teenage years. Fortunately, homozygous FH is much less prevalent, occurring in one in 250,000 to 1 million individuals.

Underutilization of cascade screening

The United States Preventive Services Task Force recommends blood cholesterol screening in all adults [4]. In 2011, NHLBI and the American Academy of Pediatrics likewise urged universal screening of children between the age 9–11, even earlier when strong family history of premature heart disease is present [5]. Familial aggregation of CHD accounts for approximately half of individuals who experience acute coronary syndrome [6]. This was the rationale for an earlier recommendation for targeted cholesterol screening of children based upon positive family history of premature CHD, or known parental total cholesterol >240 mg/dl. Retrospective analysis of over 20,000 West Virginia fifth grade children who participated in a school-based universal risk factor screening program, including fasting lipid profile, revealed that over a third of children with moderate to severe elevation of LDL-C >160 mg/dl would not have been identified by targeted screening criteria [7]. It is not that family history of premature CHD is an unimportant determinant of risk. Rather, in today's society it is often not completely available.

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The observation that individuals who experience acute coronary syndrome are as likely as not to have normal blood cholesterol may contribute to physician behavior regarding family-based cascade screening. Among practitioners today it is rarely a consideration. A systematic literature review of behaviors of relatives of people with premature heart disease, as well as physicians, provides some insight about why cascade screening is not widely implemented [8]. Within a family in which premature heart disease is prevalent, first-degree relatives do not sufficiently understand the importance of heredity as a risk factor for heart disease. Affected individuals therefore underestimate their own vulnerability, and they are often unable to sustain risk-reducing behaviors. The failure of physicians to recommend family-based screening is strongly related to lack of control of the healthcare of the family as a whole. In contrast with decades past, rarely do closely related family members share the same healthcare provider. FH presents the additional challenge of being underestimated in terms of prevalence, autosomal inheritance pattern and increased risk, as is evidenced by a 2011 survey [9]. The survey of American College of Cardiology members revealed that approximately 80% of them were unaware how common FH is, 60% did not realize that first-degree relatives have a 50% chance of also having FH and none knew that individuals with FH had a 20-fold risk of developing premature CHD. The unfortunate result is underutilization of cascade screening to diagnose FH, and subsequent lack of treatment proven to be highly effective in decreasing morbidity and mortality from FH-related CHD.

The European experience

Several European nations have demonstrated the utility of population-wide surveillance of lipid status to set the stage for cascade screening of relatives of index cases with FH. The key to their success is community-oriented programs in which, following informed consent, healthcare workers make home visits to at-risk families.

In The Netherlands, following identification of individuals with probable FH based upon standard clinical criteria, arrangement is made by telephone to visit the home and obtain blood samples for lipid measurement and DNA analysis among family members. Over 5000 relatives are screened annually, resulting in identification of 1500–2000 new cases of FH per year. After 2 years of follow-up, 80% of subjects remained adherent to drug therapy [10].

Similarly, NICE in the UK promotes cascade screening for relatives of patients with FH. Genetic confirmation of defects in the *LDLR* gene are present in three-quarters of suspect cases, and mutations of the *APOB* and *PCSK9* are found in 5.5 and 1.5%, respectively. The British data documents that not only are more FH patients being diagnosed earlier, but treatment with statins has resulted in an 80% reduction in risk of initial-onset CHD [11].

In Spain, a study by the Foundation for Familial Hypercholesterolemia demonstrated that cascade screening resulted in earlier identification of FH and longer survival. Initiation of pharmacologic treatment extended life expectancy, shifting the cost curve in favor of a national program of screening to reduce the impact of cardiovascular disease [12].

Investigators conducting FH screening in Scotland studied two different approaches to access relatives of FH patients and found contrasting results. The 'direct' approach in which a member of the healthcare team contacted the relatives was perceived as more threatening than an 'indirect' approach in which the patient encourages DNA screening of their relatives. However, though indirect contact was more acceptable this approach yielded fewer participants [13].

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Ethicists have raised questions about cascade screening [14]. Do relatives of FH index cases feel pressured to agree to screening; does it compromise their autonomy or invade their privacy? It is pointed out that standard practice in clinical genetics is proband-initiated contact of relatives. The question is raised whether direct contact by professionals is justifiable. A suggested compromise is that a two-step approach be used in which direct contact is made only after initial family contact has been established.

Foundation support of cascade screening

Critical success factors for the successful implementation of FH cascade screening have been identified in The Netherlands and a number of other nations with advanced programs [15–17]. A professional association that disseminates information about the relevance and need for systematized cholesterol screening is extremely helpful, as is a regionalized system of lipid clinics. Insurance coverage for these preventive services, including governmental support of electronic data system querying, is an important requirement. Of great importance is a patient-centric FH advocacy organization as a means of raising awareness among the lay population. Patient support groups facilitate dialog with other patients in similar circumstances, as well as acquisition of up-to-date information about clinical trials and new treatments. Such an organization now exists in the USA.

The Familial Hypercholesterolemia Foundation (FH Foundation) is a nonprofit organization with the goal of advancing identification and treatment of this life-threatening genetic disease [18]. Patient led, it seeks to raise awareness through education and enhance care by promoting research. Fundamental to achievement of this goal has been the creation of the CASCADE FH Registry, a collaborative effort between providers, academics and patients with FH in which enrollment is facilitated by a hybrid process involving its various constituents.

Future perspective

It is estimated that less than 1% of the 600,000 to 1.2 million individuals in the USA with FH have been identified. This contrasts with the fact that 75% of all such individuals in The Netherlands have been diagnosed. The potential for impact on risk reduction for CHD in the USA is enormous, but it can only reach fruition if it becomes national public health policy. A first step is to adopt the recommendation of the FH Foundation and the National Lipid Association to designate separate ICD-10-CM codes for heterozygous and homozygous FH to distinguish this genetic disease from other causes of hyperlipidemia. Current guidelines underscore the need to distinguish individuals with LDL-C >190 mg/dl because of the high probability of genetic etiology, specifically FH. Aggressive treatment is indicated, as well as cascade screening of family members.

Clinicians attempt to optimally treat their individual patients with elevated cholesterol, especially those with documented CHD. But some have claimed "I am not particularly concerned about why their levels are high." A few of these patients will have FH. Most of them have children. Half of these children will also have FH, and early treatment with lifestyle modification and cholesterol lowering medication will provide them the opportunity for longer, healthier life. Failure to identify and treat will likely negate this bright future.

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