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STATE-OF-THE-ART PAPER

The Severe Hypercholesterolemia Phenotype

Clinical Diagnosis, Management, and Emerging Therapies

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The severe hypercholesterolemia phenotype includes all patients with marked elevation of low-density lipoprotein cholesterol (LDL-C) levels. The most common cause is autosomal dominant hypercholesterolemia, an inherited disorder caused by mutations either in *LDL receptor*, apolipoprotein B (*APOB*), or proprotein convertase subtilisin kexin type 9 (*PCSK9*) genes. However, it is now known that many subjects with severe inherited hypercholesterolemia have no defects in these genes. These cases are caused either by mutations in genes yet to be identified or are consequences of polygenic, epigenetic, or acquired defects. Because the clinical consequences of extreme hypercholesterolemia are the same no matter the cause, the focus should be on the identification of subjects with severe hypercholesterolemia, followed by phenotypic screening of family members. Genetic screening is not necessary to diagnose or initiate treatment for the severe hypercholesterolemia phenotype. Management of severe hypercholesterolemia is based on risk factor modification and use of multiple lipid-lowering medications. Lipoprotein apheresis is indicated for coronary artery disease (CAD) patients taking maximally tolerated therapy and with LDL-C levels >200 mg/dl (>300 mg/dl if without CAD). A microsomal triglyceride transfer protein inhibitor and an antisense oligonucleotide against APOB have recently been approved for use in subjects with clinically diagnosed homozygous familial hypercholesterolemia. PCSK9 inhibitors, currently in phase II and III trials, lower LDL-C up to an additional 70% in the setting of maximally tolerated medical therapy and have the potential to reduce LDL-C to <70 mg/dl in most patients. Early identification of affected individuals and aggressive treatment should significantly reduce the burden of cardiovascular disease in society. (J Am Coll Cardiol 2014;63:1935–47)

The severe hypercholesterolemia phenotype includes all subjects with low-density lipoprotein cholesterol (LDL-C) levels above 190 mg/dl, regardless of the cause. The term autosomal dominant hypercholesterolemia (ADH) is reserved for patients with mutations in genes controlling LDL levels. Familial hypercholesterolemia (FH) is a common monogenic disorder caused by abnormalities in the LDL receptor (LDLR) protein, commonly inherited in a codominant fashion (1). Patients can be true FH homozygotes (HoFH), with 2 identical mutations; compound heterozygotes, with a different mutation in each allele; or FH heterozygotes (HeFH), with only one mutated allele. ADH includes FH and the hypercholesterolemia resulting from defects in 2 other major genes, *APOB* and *PCSK9*, which influence plasma LDL clearance by affecting the efficiency of ligand–receptor interaction. The inadequate LDL clearance manifested in all forms of ADH leads to marked elevations of plasma LDL-C levels and premature cardiovascular disease (CVD) (2). In individuals with true HoFH, the LDLR pathway is nonfunctional or markedly defective (2% to 30% activity), leading to plasma LDL-C levels 4 to 8 times above average (>500 mg/dl), whereas in patients with HeFH, the loss in receptor activity (up to 50%) leads to LDL-C levels 2 to 3 times above average (3). Many individuals with LDL-C >190 mg/dl do not have defects in any of the 3 genes. A polygenic origin is likely in many of these cases (4), and thus, genetic screening strategies are not easily endorsable as they pose great challenges to comprehensive, effective, and economical implementation. Because the risk of vascular disease is determined by lifelong exposure to hypercholesterolemia, not by the genotype that produces it, we propose that screening should focus on identifying subjects with the phenotype without investing resources in the identification of the genetic causes, as also suggested in a recent editorial by Stein and Raal (5).

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Abbreviations and Acronyms

ADH = autosomal dominant hypercholesterolemia

APOB = apolipoprotein B

CAD = coronary artery disease

CHD = coronary heart disease

FH = familial hypercholesterolemia

HeFH = heterozygous familial hypercholesterolemia

HoFH = homozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LDLR = low-density lipoprotein receptor

Lp(a) = lipoprotein(a)

This review summarizes the state-of-the-art in the identification of subjects with the severe hypercholesterolemia phenotype and ADH, screening of affected family members, and established and emerging treatments.

Prevalence of Severe Hypercholesterolemia Phenotype and Risk of CHD

Approximately 600,000 people in the United States and between 14 and 35 million people worldwide manifest the severe hypercholesterolemia phenotype (2,6). HeFH is estimated to occur in 1 of every 200 to 500 persons, with approximately 10 million affected worldwide, and the frequency may vary among certain populations because of gene founder effects. True HoFH is rare, with a supposed prevalence of approximately 1 per 1,000,000 persons.

The risk of premature coronary heart disease (CHD) is estimated to be approximately 20-fold higher in untreated FH patients than in control subjects (Fig. 1) (7). Fatal or nonfatal coronary events occur in approximately 50% of males before age 50 and 30% of females before age 60. In subjects with HoFH, sudden death, acute myocardial infarction (MI), or need for revascularization may occur in patients in the first decade of life (8,9). HoFH also commonly causes aortic stenosis, both valvular and supravalvular, due to lipid deposition in the aortic valve leaflets and aortic root (10). The prevalence of HeFH is higher among patients with MI, from ~5% of patients <60 years of age to almost 20% in patients <45 years of age (11–13). Additional risk factors such as smoking, hypertension, diabetes, male sex, and low HDL-C (14) further amplify CHD risk by 2- to 3-fold (15). In addition, elevated lipoprotein (a) (Lp[a]) levels are common in FH patients, and the trait seems to be a consequence of FH and is not inherited separately (16,17). Given that the evidence to date does not suggest that the LDLR is involved in Lp(a) clearance (18,19) this suggests that overproduction of APOB, known to occur in FH (20–23), may be partially responsible for the overproduction of Lp(a) particles.

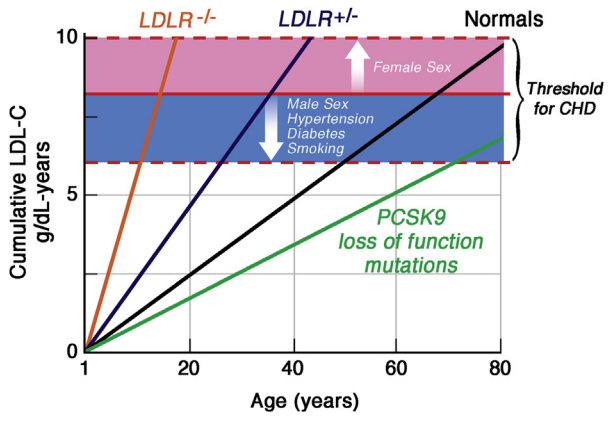

Figure 1 Relationship Between Age and Cumulative LDL-C Exposure

Coronary heart disease (CHD) risk is estimated for homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH), and age-adjusted low-density lipoprotein cholesterol (LDL-C) levels in normal individuals. The **horizontal red line** represents a theoretical threshold of the cumulative LDL-C exposure required for development of CHD. The **height of the red line** will be lower in the presence of additional CHD risk factors. Reprinted with permission from Horton et al. (7).

Genetics

Our physiological understanding of FH is based on the pioneering work of Brown and Goldstein (1), who established a molecular link among defects in the *LDLR* gene, loss of function of LDLR, the cell surface protein that binds and internalizes LDL particles, and the inherited hypercholesterolemic trait (1). Although classic FH is still defined as severe hypercholesterolemia caused by a defect in the LDLR, a functionally similar effect is caused by mutations in *APOB* (the ligand for LDLR) or PCSK9 (the terminator of LDLR lifecycle) (Fig. 2, Table 1) (24,25), all of which significantly impair the function of the LDLR pathway. Mutations in LDLR are responsible for approximately 85% to 90% of cases of clinical FH, and >1,600 mutations have been documented to date (26). Common mutations in the *LDLR* gene include deletions, insertions, and missense and nonsense changes affecting all of the major steps in LDLR trafficking and function (Fig. 3) (reviewed in Hopkins et al. [2]). A less common mutation in APOB leading to poor interaction with the LDLR (27) is responsible for a phenotype indistinguishable from classic FH, except for less drastic elevations in LDL-C. Additionally, ultrarare monogenic defects can cause severe autosomal recessive hypercholesterolemia, caused by defects in a liver-specific LDLR chaperone LDLR adaptor-related protein 1 (LDLRAP1) (28) and beta-sitosterolemia due to the abnormal intestinal absorption of plant sterols (29), both of which are recessively inherited.

PCSK9 is a secreted convertase that binds to the LDLR and targets it for lysosomal degradation mostly in the hepatocyte. Gain-of-function mutations in PCSK9 leading to elevated plasma LDL-C levels are an uncommon cause of FH (30). Interestingly, subjects with loss-of-function mutations in PCSK9 have reduced plasma levels of LDL-C and are significantly protected from coronary heart disease (CAD) (31). Indeed, the extent of protection is