

Familial Hypercholesterolemia and Early-Onset Coronary Heart Disease – an Overview

Introduction

Familial hypercholesterolemia (FH) is a dominantly inherited disease affecting 1 in 500 individuals (see reference 1 for review). FH leads to coronary heart disease (CHD) by age 60 in half of affected men and a third of affected women and causes a 50 fold (in men) to 125 fold (in women) increased risk of myocardial infarction before age 40 (see reference 2 for review). Atherosclerosis due to FH often starts in childhood, but remains asymptomatic until CHD develops (3). While FH is a treatable disease, it is widely under-diagnosed and undertreated, leading to thousands of preventable deaths per year in the US alone (4-7).

Since FH has been linked to autosomal dominant loss-of-function mutations in the genes *LDLR* or *APOB* (see reference 1 for review), genetic testing can allow a diagnosis of FH. Genetic “cascade” screening of relatives of FH patients has been shown to be a sensitive, specific, and cost effective method for increasing diagnosis and treatment levels for FH (8-11).

Molecular Pathophysiology

The gene *LDLR* codes for the low density lipoprotein receptor, which mediates clearance of low-density lipoprotein (LDL), the main plasma reservoir for cholesterol, from the plasma. Lipoproteins are globular particles composed of a core of triglycerides and cholesteryl esters and a surface layer of phospholipids and free cholesterol, into which one or more proteins (apolipoproteins) are inserted. Lipoproteins serve to transport cholesterol and other lipids through the aqueous plasma, allowing exchange of lipids between lipoproteins and cells as well as between different types of lipoproteins. Classification of lipoproteins is based on their specific density, which reflects their protein and lipid composi-

tion. Low-density lipoprotein (LDL) is particularly rich in cholesterol and contains one principal apolipoprotein (apolipoprotein B-100 or ApoB). Binding of ApoB, encoded by the gene *APOB*, to LDLR leads to internalization of the LDLR-LDL complex. While LDLR is subsequently recycled to the membrane, LDL is disassembled into its components. In the liver, cholesterol derived from LDL is excreted in the bile, either as free cholesterol or as bile acid. Cholesterol derived from disassembled LDL also inhibits cholesterol biosynthesis within the cell.

Pathogenic sequence variants in *LDLR* or *APOB* decrease the ability of liver cells to clear LDL from the plasma. Excess LDL accumulates in arterial walls, where it is oxidized and taken up in a non-saturable manner by macrophages, leading to development of atherosclerotic lesions and, over time, atherosclerotic plaques.

If only one of the two *LDLR* genes present in each somatic cell is affected by a mutation (heterozygous FH), the removal rate of LDL from the blood is reduced by half, leading to a doubling in the plasma LDL cholesterol level. If both *LDLR* genes are mutated (homozygous FH), plasma LDL cholesterol levels are increased fivefold or more. Compound heterozygosity for mutations in one copy of the *LDLR* gene and one copy of the *ApoB* gene also lead to more severely elevated plasma LDL cholesterol levels.

Clinical Presentation and Diagnosis

Heterozygous FH often first presents with symptoms of CHD in the fourth or fifth decade of life. Cholesterol levels are elevated from birth, but can overlap with those of the normal population (12). Diagnostic cut-off points are therefore difficult to set, especially in children and adolescents, where cholesterol levels are age-dependent (13). While strict clinical criteria allow high specificity of diagnosis, they

result in low sensitivity. Tendon xanthoma, e.g., are highly diagnostic of FH, but do not affect all patients and often do not develop until later in life (14). Use of relaxed clinical criteria increases the sensitivity of diagnosis, but significantly reduces the specificity (12). Even among family members of FH patients, a diagnosis based on cholesterol measurement alone is missed or wrongly assigned in 10-20% of cases (8,12). In contrast, genetic testing shows close to 100% specificity and sensitivity for identifying carriers among relatives of FH patients, once the familial mutation is known (14). Genetic testing also allows a definitive diagnosis of FH in the proband and is therefore considered the “gold standard” for diagnosis of FH. Cost-effective indications for genetic testing include symptoms of CHD before age 45 in men and before age 55 in women; greatly elevated serum cholesterol levels at any age; and family history of premature CHD or of significant hypercholesterolemia (11). In the proband for a family, sequencing of the entire coding region of *LDLR* is indicated, since hypercholesterolemia-associated mutations are scattered throughout the gene (15). Once a familial *LDLR* mutation has been identified, gene sequencing can be limited to the region where the mutation is located to identify other affected family members among the children, parents, or siblings of the proband. All known hypercholesterolemia-associated mutations in *APOB* are located in a 200-nucleotide region (see reference 1 for review).

Homozygous FH typically presents with planar xanthomata by age six, symptoms of CHD by age 10, and, if untreated, leads to myocardial infarction by age 20.

Treatment

Treatment options for heterozygous FH include dietary restriction of cholesterol and saturated fat and/or administration of statins (HMG-CoA reductase inhibitors), ezetimibe (a selective inhibitor of intestinal absorption of dietary and biliary cholesterol), bile acid sequestrants, or niacin. Most of these interventions are aimed at depleting liver cells of cholesterol, which acts as a feedback inhibitor of LDLR expression. Lower levels of cholesterol in the liver cells lead to an increase in the number of LDLR molecules expressed on the cell surface, improving plasma clearance of LDL. If statins are not tolerated or not effective, ileal bypass surgery to decrease reabsorption of bile acids from the gut or extracorporeal apheresis combined with LDL immunoabsorption may be considered. Homozygous FH is treated with extracorporeal apheresis or liver transplantation.

Diet and lifestyle changes are generally recommended as the first-line treatment for hypercholesterolemia, especially in children. However, in individuals with FH, diet and lifestyle changes alone are rarely effective, and pharmacological intervention may have to start in childhood (see reference 16 for discussion). Statin therapy has been shown to lead to significant regression of existing carotid atherosclerosis in both children and adults with pathogenic mutations in *LDLR* or *APOB*, and no adverse effects on growth, sexual maturation, hormone levels, or liver or muscle tissue were observed during up to two years of statin treatment in children (17-21).

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