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Other forms of primary hypercholesterolemia. Familial combined hyperlipidemia and polygenic or common hypercholesterolemia

Otras formas de hipercolesterolemia primaria. Hiperlipidemia familiar combinada e hipercolesterolemia poligénica o común

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Familial combined hyperlipidemia (FCHL) is a primary dyslipidemia whose prevalence ranges between 1 and 3%, although it is more frequent in patients with coronary artery disease. FCHL is found, for example, in 20% of those under 60 years old who survived an acute myocardial infarction and up to 38% in those survivors under 40 years.[1,2] Due to the lack of robust diagnostic markers, in many patients at high risk of some type of atherosclerotic cardiovascular disease (ASCVD), the diagnosis of FCHL is not established. This dyslipidemia has been characterized as a hereditary disorder (oligogenic, i.e., caused by just a few genes), autosomal, with variable penetrance. Several genetic abnormalities have been signaled as responsible for FCHL, encompassing various clinical lipoprotein phenotypes. The lipid profile of FCH is rather heterogeneous, which suggests a multifactorial origin in which a variety of genetic abnormalities lead to various pathogenic alterations of lipoproteins and their metabolism. It has been identified the gene that encode the upstream transcription factor 1 (USF1) as one of the principal contributors to this pathology.[3] USF1 regulates the expression of multiple genes involved in glucide and lipid metabolism. When it is inactivated in mice, brown adipose tissue is activated, enhancing thermogenesis, decreasing triglyceridemia, and reducing insulin resistance and its manifestations, as lipid pathology and fatty liver disease.[4] Mexican population, with a high rate of abdominal obesity and insulin resistance, is prone to suffer combined dyslipidemia and the lipid triad. In fact, several Mexican families have been found affected with FCHL.[5,6]

The genetic disorder helped by unhealthy lifestyle (high fat diet and sedentarism) increase the hepatic formation of VLDL, small and dense LDL particles, and apo B100. Frequently, FCHL is associated to low concentrations of the protective lipoprotein HDL, combination that is known as atherogenic dyslipidemia or lipid triad. This combination can be also secondary to obesity/diabetes phenotypes, and whose atherogenic power has been unveiled many years ago.[7-9]

As a heterogeneous, highly pleiomorphic dyslipidemia, and still without well-defined genetic alterations, universally accepted diagnostic criteria are lacking.[2] Therefore, the clinical approach demands the exclusion of secondary causes of combined dyslipidemia. As the phenotypic expression differs from patient to patient, the concentrations of total cholesterol (TC) and triglycerides (TG) in members of the same affected family show a great variability.[8] The following could be valuable diagnostic clues, although none of them is indispensable or specific: 1) Familial history of premature ASCVD (atherosclerotic events occurring in men

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under 55 years old, or in women under 65 years). 2) Familial history of dyslipidemia (two or more first degree relatives with some type of dyslipidemia). 3) Combined total and LDL hypercholesterolemia (> 240 and > 160 mg/dL, respectively) plus hypertriglyceridemia (> 200 mg/dL). In general, concentrations of TC and LDL are not strikingly elevated, as in familial hypercholesterolemia. Concomitant hypoalphalipoproteinemia (HDL-c less than 40 mg/dL) is common. Hypertriglyceridemia stimulates the production of small and dense LDL particles, highly oxidizable and atherogenic. 4) Apolipoprotein B100 elevated (> 120 mg/dL). 5) Absence of clinical or biochemical data signaling secondary causes of combined dyslipidemia as hypothyroidism, nephrotic syndrome, chronic kidney disease, pheochromocytoma, Cushing syndrome or steroids consumption, and use of drugs like retinoids, and some antiretroviral agents, among many others. 6) Absence of tendinous xanthomas. 7) Genetic studies: gene encoding USF1, and members of the gene cluster APOA1/C3/A4/A5, that influence lipid metabolism, among others under scrutiny.[1,2,9-11]

The relationship between this hereditary dyslipidemia and the physiopathological clinical complex composed by obesity/overweight, insulin resistance, and diabetes mellitus, is unclear. Very probably there is a bilateral and complementary connection, in which the lipid pathology caused by defective genes is magnified by the metabolic abnormalities secondary to the insulin resistance/hyperinsulinism binomial and diabetes syndromes. Contrariwise, persons with FCHL also have the propensity to develop abdominal dysmetabolic adiposity, insulin resistance and diabetes. Modest increases in weight and insulin resistance were associated with significantly higher probability of FCHL in a multi-ethnic US population. The multi-ethnic study of atherosclerosis (MESA) showed that in various ethnic groups, a modest increment of weight has different consequences in the development of combined dyslipidemia,[12] what seems indicate again the intricate binomial interaction between genes and environment.[13] The therapeutic management of this dyslipidemia follows the same general principles of the treatment of hypercholesterolemia and hypertriglyceridemia, reviewed in other sections of this text.

POLYGENIC OR COMMON HYPERCHOLESTEROLEMIA

Polygenic hypercholesterolemia is a frequent cause of elevated blood cholesterol secondary to multiple gene mutations, expressed as single nucleotide polymorphisms (SNPs), powerfully influenced by environmental factors, mainly diet rich in animal fat. Although they had already been identified 95 loci significantly associated to lipid anomalies,[14] more recently, the Global Lipids Genetics Consortium (GLGC) found 62 more for a total of 157.[15] Studies aimed to distinguish between polygenic and familial hypercholesterolemia (FH), have shown that only in 40-60% of patients with clinical FH can be demonstrated a monogenic defect, which involves the LDLR, Apo B or PCSK9 genes.[16] A major discovery was the finding that in many patients with FH the genetic disturbance was not monogenic but in essence polygenic.[16-18]

The genetic participation in common hypercholesterolemia, does not lessen the crucial role of lifestyle, environmental, and other metabolic factors, that greatly contribute to rise LDL-c concentrations, especially in the later stages of life. But due to genetic influence, the frequency of this type of dyslipidemia is higher in subjects with familial history of ASCVD. By having LDL concentrations lower than monogenic hypercholesterolemia, and because in the polygenic form, the lipid disorder appears late in life, the ASCVD episodes are also later (> 50 years of age), being, in general, less lethal that FHC. However, for being much more frequent the polygenic than the monogenic form, the epidemiologic impact of the former in the genesis of ASCVD is more important. A fact worth noting is the best therapeutic and dietary response of the polygenic form.[19]

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