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Primary hypercholesterolemia
Familial hypercholesterolemia

Hipercolesterolemia primaria
Hipercolesterolemia familiar

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INTRODUCTION

Cardiovascular diseases (CVD) represent the main cause of death in the world. An estimated 17.9 million people die each year from these diseases worldwide. One of the main cardiovascular risk factors is hypercholesterolemia.[1] Basically, the causes of this dyslipidemia are divided into two large groups: primary and secondary. The primary causes are those that have a genetic origin; while hypercholesterolemia due to secondary causes is one that occurs because of another diseases or causes, such as diabetes, liver disease, kidney failure, nephrotic syndrome, hypothyroidism, the consumption of certain drugs (antiretrovirals, corticosteroids, etc.), autoimmune diseases, or a high-fat diet, among others.[2]

Of the primary, due to pure or predominant genetic causes, the most common is familial hypercholesterolemia (FH) (OMIM 143890), a disease with an autosomal dominant inheritance pattern, characterized by the fact that affected patients have very high blood cholesterol levels from birth, accelerated atherosclerosis, and thus a very high risk of premature death from CVD.[3]

Based on recent meta-analyzes and what has been published on populations for which data are available, a prevalence of 1 in 310 individuals in the general population has been estimated. Therefore, this disease represents the first cause of premature CV death of genetic cause.[4] Due to the high frequency and seriousness of its consequences, since 1998 the World Health Organization (WHO) classified it as a World Public Health Problem, that should be integrated into the screening programs of all populations, for a detection and timely treatment.[5]

FAMILIAL HYPERCHOLESTEROLEMIA

FH is caused by mutations in the LDLR (19p13.2), APOB (2p24.1) and/or PCSK9 (1p32.3) genes. These genes code for proteins that participate in the metabolism of low-density lipoprotein cholesterol (LDL-c), for which mutations in any of the three alter their homeostasis, causing an increase in serum concentration, a rise in cholesterol deposits in some tissues, and the development of atherosclerotic lesions, in turn responsible for cardiovascular syndromes.[6]

The main cause of FH is due to mutations in the LDLR gene, which codes for the LDL-c receptor, which is located on the plasma membrane of all cells, mainly that of hepatocytes. To date, more than 2000 variants distributed throughout the entire gene have been described, which could cause an alteration in the function or a decrease in the number of receptors to internalize LDL-c, what in turn causes raises in its serum concentration.[7] The APOB gene encodes apolipoprotein B, which serves as a ligand between LDL-c and its receptor, which allows to internalize the lipoprotein inside the cell, to be metabolized.

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Therefore, mutations in this gene, even without defects in the receptors, also cause hypercholesterolemia. Unlike the large number of mutations found in the LDLR gene, only very few have been reported in the APOB gene, which are generally found in exon 26 and 29, which is the coding part for receptor binding. The PCSK9 gene encodes a protein that when it binds to the LDL receptor allows lysosomes to degrade it, so mutations that cause a «gain of function» generate an excessive production of the protein, decreasing in this way the number of receptors for LDL-c and consequently provoking hypercholesterolemia.[7,8]

HETEROZYGOTE AND HOMOZYGOTE FH

In addition to severe hypercholesterolemia from birth and premature atherosclerosis, some patients with FH may have accumulation of cholesterol in other parts of the body, such as eyelids, eyes, and tendons, causing additional clinical manifestations such as xanthelasma, corneal arch and xanthomas, respectively *(Figure 1)*. Based on the clinical and biochemical characteristics, classically, patients have been classified into two large groups: heterozygous and homozygous. Heterozygous patients have 2 to 3 times the normal levels of LDL-c, and without adequate treatment, most will suffer CVD between 30-50 years old. Xanthelasma, corneal arch and xanthomas, usually appear from the second decade of life. Unfortunately, only a low percentage of patients have these extravascular manifestations, which makes early detection of the disease difficult.[9] The clinical and biochemical characteristics of homozygous patients are much more serious. LDL-c levels are 5 to 10 times above normal values, causing signs and symptoms of CVD at early ages, even since childhood. Most of these patients without treatment, die before the age of 30. Unlike heterozygotes, most homozygous patients present xanthelasma, corneal arch and xanthomas from the first decade of life, thus favoring detection. Fortunately, the prevalence of homozygous patients is much lower, ranging from 1 in 250,000 to 1 in 1,000,000.[10]

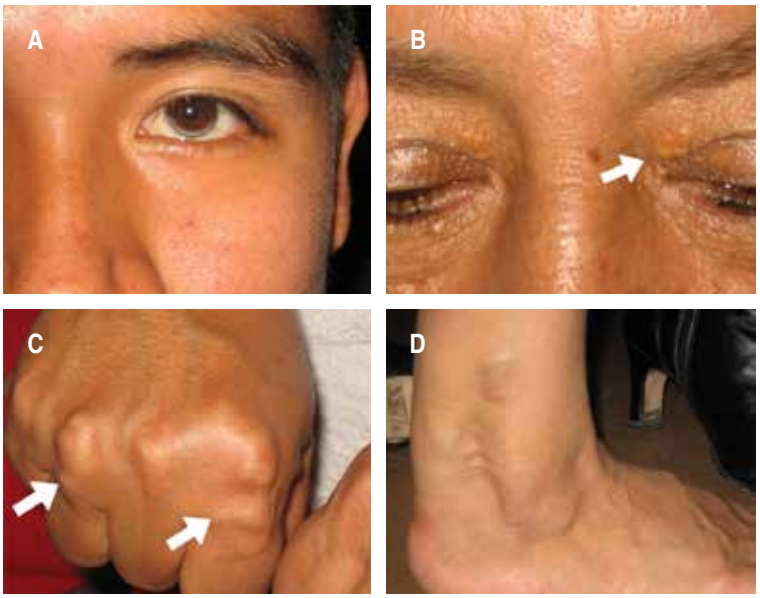

Figure 1: Clinical characteristics of familial hypercholesterolemia: **A)** Corneal arch. **B)** Xanthelasma. **C)** Xanthomas in tendons of the fingers of the hands. **D)** Xanthoma in the Achilles tendon.

Thanks to advances in the knowledge of the molecular bases of FH, patients with clinical and biochemical characteristics of homozygous variety are classified into three groups: true homozygous, compound heterozygous, and double heterozygous. True homozygotes are those that present the same mutation in each of the two alleles of the same gene, either in the LDLR, APOB or PCSK9 gene. Compound heterozygotes show different mutations in each of the two alleles of the same gene. Finally, double heterozygotes are those that have one of the two mutated alleles in a gene and another of the two mutated alleles of another gene.[9]

CLINICAL, BIOCHEMICAL, AND MOLECULAR DIAGNOSIS

In most cases, the diagnosis is established based on clinical and biochemical criteria and through family study. However, for some patients, especially in those who do not have a family history or who do not meet sufficient criteria, a molecular study will be required to identify the genetic cause and thus diagnostic confirmation.[6,11] The diagnostic criteria based on scores help to establish the diagnosis in the index case. The most used are those of the Dutch Lipid Clinic Network Diagnostic Criteria and those of the English Simon Broome Registry.

FH should be suspected in all those adults who have total cholesterol levels above 300 mg/dL and/or LDL cholesterol levels above 190 mg/dL; in patients who have CVD manifestations before the age of 60 and/or clinical signs of hypercholesterolemia, such as xanthomas, xanthelasma and/or corneal arch. The cut-off point for LDL-c level for suspected FH in children and adolescents is ≥ 160 mg/dL.[3,9]

Therefore, the diagnostic criteria for FH can be summarized in three points: 1. Severe hypercholesterolemia at the expense of LDL-c, once secondary causes such as hypothyroidism, kidney and liver damage, consumption of certain drugs, among others, have been ruled out.[2] 2. Presence of premature CVD, xanthomas, xanthelasma and/or corneal arch and 3. History of relatives with severe hypercholesterolemia and premature CVD. The study of relatives is extremely important, since it allows to corroborate the vertical transmission of the disease (autosomal dominant inheritance) and also the detection of other members of the family, that is, the diagnosis through the cascade screen.[3,12,13]

GENETIC COUNSELING

Being a disease with an autosomal dominant inheritance pattern, the theoretical risk for the offspring of a heterozygous index case is 50% and 100% for a homozygous index case. Given that it is a disease whose fatal consequences can be prevented with timely and adequate treatment, when identifying an index case, it is required to do the «cascade screening», that means that all first-degree relatives must be studied as far as possible, and once another affected individual has been identified, his or her offspring must be screened, and so on. Screening for FH is not recommended in children under two years of age, as to date, there is no treatment approved for such age. The cascade sieve is more effective, when the molecular study is available.[14] It should be noted that there is a form of autosomal recessive inherited hypercholesterolemia (ARH), which is caused by mutations in the LDLRAP1 gene, which encodes for a protein that participates in the internalization of the LDL-LDL receptor complex. It is important to suspect this type of hypercholesterolemia in those patients who have a healthy parents or when consanguinity and inbreeding are documented. The risk of recurrence for this type of hypercholesterolemia is 25%.[15]

TREATMENT

The goal of treatment is to lower cholesterol levels to normal levels, in order to reduce cardiovascular risk, indefinitely. Diet and lifestyle modifications are important, but not sufficient to achieve a significant decrease in cholesterol in these patients, which in consequence require lipid-lowering drugs. In heterozygous patients, the drugs of choice are potent high-dose statins, alone or in combination with other oral lipid-lowering drugs, as ezetimibe. The dose will depend on the baseline values of LDL-c and the response to treatment of everyone, requiring indefinitely monitoring by a multidisciplinary team. The therapeutic goal for adults is 100 mg/dL of LDL-c, but if the patient has additional cardiovascular risk factors, treatment must be more stringent to reach < 70 mg/dL or less. Many heterozygous patients achieve these figures with conventional drugs, as statins and PCSK9 inhibitors. However, as most of homozygotes do not have any LDLR activity or it is greatly reduced, drugs that upregulate LDL receptor expression have less or null efficacy. Also, homozygous patients frequently have LDL-c levels above 600 mg/dL, so it is more difficult to achieve the therapeutic goals. These patients require other therapeutic measures, some of them invasive, such as LDL-c apheresis. In recent years, new drugs have been developed for the treatment of FH, designed especially for those patients who do not respond to traditional drugs, alongside monoclonal antibodies for PCSK9, there are antisense oligonucleotides for apolipoprotein B and finally MTP protein (microsomal triglyceride transfer protein) inhibitors, among others.[3,9,10,12]

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