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Research Article

An Expanded View on the Importance of Early Diagnosis of Family Hypercholesterolemia

Zorzo RA[1]*, Honorato ALSC[2], Suen VMM[3] and Liberatore RDR JR[4]

[1]Professor of Faculty of Medicine of Estacio University, Ribeirão Preto and Post-graduation Student (PhD Level) by Children and Adolescents Health in Ribeirão Preto Medical School, São Paulo University, Brazil

[2]Post-Graduation Student (PhD Level) by Internal Medicine Department in Ribeirão Preto Medical School, São Paulo University, Brazil

[3]Professor from the Department of Internal Medicine, Division of Nutrology, Ribeirão Preto Medical School, University of São Paulo

[4]Professor Associated in Pediatrics Department in Ribeirão Preto Medical School, São Paulo University, Brazil

***Corresponding Author:** Zorzo RA, Professor of Faculty of Medicine of Estacio University, Ribeirão Preto and Post-graduation Student (PhD Level) by Children and Adolescents Health in Ribeirão Preto Medical School, São Paulo University, Brazil.

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Abstract

Familial hypercholesterolemia (FH) is an autosomal codominant disease that has an estimated prevalence of 1:500 in general population. When not diagnosed early, its outcomes in coronary artery and brain disease tend to have an early presentation, with a high risk of death. Its origin is related to a mutation in the LDLR, APOB and PCSK9 genes, and possibly epigenetic alterations as well. This study aimed to review the last five years of the literature on the disease in pediatric age.

Keywords: *Expanded; Importance; Diagnosis of Family; Hypercholesterolemia*

Introduction

Dyslipidemias are defined as alterations in the plasmatic levels of lipids, either above or below the considered normal range. The concern with diagnosing dyslipidemia at an early age is since it is a situation that increases the risk of atherosclerosis, and its pathological outcome, which is the increase in mortality from vascular disease [1,2].

Atherosclerotic disease is a public health concern, since the pathophysiological process is silent, and approximately half of the individuals who carry the morbidity present an acute coronary event, with a real risk of death, as the first clinical manifestation. The two highest adult mortality rates in Brazil in 2017 were ischemic heart disease and cerebrovascular disease (80.0% and 56.6% respectively), two clinical manifestations that result from atherosclerosis [1,2].

Several studies have shown that disease manifestations are present in young populations sufficiently exposed to risk factors, especially those with obesity and severe hypercholesterolemia-related diseases. Typical lesions of atherosclerosis have already been identified in children, such as increased thickness of the carotid intima-media layers on ultrasonography of obese children [3,4].

Dyslipidemias can be classified, according to their etiology, into primary or secondary [5].

Familial Hypercholesterolemia (FH) is the most common primary cause of dyslipidemia in children. It is a genetic disease of lipoprotein metabolism, whose inheritance is autosomal dominant, and which is characterized by very high serum LDL levels since birth, the presence of characteristic clinical signs and increased risk of premature coronary artery disease [6].

Aim of the Study

This study aimed to review the disease, its pathophysiology, pathogenesis, and clinical importance.

Methodology

A search for articles with the term "Family Hypercholesterolemia" was performed in the PubMed database, in the last 5 years. In this first search, 1,868 articles were found. Of these, 940 articles were selected that had the full free text. Finally, the age of subjects from zero to 18 years old only was selected, and we reached 47 articles that made up this review.

Results and Discussion

It is estimated that, in the white population, the prevalence of heterozygous and homozygous FH is, respectively, around 1:500 and 1:1,000,000 individuals. The diagnostic criteria for FH defined for Brazil are clinical, based on the criteria of the Dutch Lipid Clinic Network [6]. In general, the presence of the HF phenotype is related to an alteration in at least one of the three genes described above, being LDLR is the most frequently affected gene.

The diagnostic criteria for FH defined for Brazil include clinical and laboratory parameters, defining the "FH phenotype". A starting point for diagnosis is considered an LDL dosage above 190 mg/dL. The diagnostic criteria, developed by the Dutch Lipid Clinic Network (DCLN), involve clinical parameters and deoxyribonucleic acid (DNA) mutation analysis. In general, the presence of the HF phenotype is related to an alteration in at least one of the three genes described above, the LDLR being the most frequently affected gene [6].

The genesis of HF is related to defects in three genes, which encode proteins with direct actions on LDL metabolism, namely: LDLR gene, which encodes the LDL cell receptor; APOB gene, which encodes Apolipoprotein B-100 which, when defective, expresses lower affinity for the LDL receptor, leading to resistance in its entry into cells and an increase in its circulating levels; PCSK9 gene, which encodes a protein responsible for the catabolism of the LDL receptor, which, when mutated with gain of function, results in accelerated destruction of the receptor, and consequent underutilization of LDL by the cell [6,7].

The penetrance of the genetic alteration approaches 100%, that is, it is enough that a single allele is altered for the phenotypic manifestation to be expressed. In these individuals, circulating LDL levels will be elevated from birth and throughout their lifetime, and will transmit the genetic defect to half of their first-degree offspring [6].

With a defective allele, the metabolism starts working with only half of its functional capacity to incorporate cholesterol into the body's cells, and when both alleles are defective, the organic use of cholesterol is minimal [6,8].

With the advancement of molecular biology techniques, it was possible to verify structural alterations in the three related genes, and in 60 - 80% of cases the detection of at least one of these genes is demonstrated. However, in 20 - 40% of patients with clinical criteria for FH, the search for genetic alterations is negative [9].

Recently, a study conducted in Ribeirão Preto, Brazil, identified a correlation between the positive methylation status of Ilha 2 of the LDLR gene and the HF phenotype in patients without structural alterations in the three canonical genes. This discovery may open a door to possible new treatment sites for hypercholesterolemic states [10].

It is estimated that in the white population the prevalence of heterozygous and homozygous FH are, respectively, around 1:500 and 1:1,000,000 individuals. Some populations are more prevalent, supposedly due to a supposed founder effect, such as South Africans (1:100), Lebanese (1:170) and French Canadians (1:270) [6].

Although there is no study specifically designed to determine the prevalence of FH in the pediatric population, it is inferred that it is the same for the general population, since it is a genetic and congenital disease. It is estimated that there are 35 million patients with FH in the world, of which 20 - 25% are children and adolescents. Statistically, 1 baby is born with HF per minute somewhere in the world [11].

The clinical picture of dyslipidemias in general is silent, not infrequently, the first manifestation is an acute coronary event [1].

However, as circulating LDL levels in FH are extremely high, physical examination findings may appear early in life. Such findings are tendon xanthomas (spherical tumors on the surface of tendons, especially the Achilles tendon), eyelid xanthelasma (yellow spots on the upper eyelids) and corneal arch (hypochromic halo present at the outer end of the iris). Such findings result from accumulation of cholesterol in these sites and, although they are not pathognomonic for FH, they strongly suggest it when present, especially when present before 45 years of age [6].

FH carriers, when not diagnosed in a timely manner, evolve with a high risk of developing early CAD, typically in the sixth decade of life in the case of heterozygotes, and in the end of the second decade in the case of homozygotes. Without treatment, 50% of men and 12% of women with FH will develop CAD before age 50, and 85% of men and 50% of women will have a cardiovascular event before age 65 [7,8].

The laboratory diagnosis of FH starts with the determination of the lipid profile. Heterozygous individuals tend to develop serum LDL levels above 300 mg/dL, while homozygous individuals can exceed 1,000 mg/dL. In patients younger than 20 years with serum LDL greater than 190 mg/dL, the probability of the existence of FH reaches 80% [1,7,8].

The diagnostic criteria for FH defined for Brazil include clinical and laboratory parameters, defining the "HF phenotype". A starting point for diagnosis is considered an LDL dosage above 190 mg/dL. The diagnostic criteria, developed by the Dutch Lipid Clinic Network (DCLN), involve clinical parameters and deoxyribonucleic acid (DNA) mutation analysis, and are described in table. In general, the presence of the HF phenotype is related to a change in hair. minus one of the three genes described above, with LDLR being the most frequently affected gene [6].

Population screenings were a very efficient strategy for the search and early detection of patients at risk. There are two strategies that can be used: universal tracking and cascading tracking [6,7].

Universal screening predicts that all children over 10 years of age should have their lipid profile collected, regardless of clinical history or family history. However, the examination must be performed at two years of age in the following situations: a) when there is a family history of premature atherosclerotic disease (before 55 years in men or before 65 years in women) and/or dyslipidemia; b) if the child itself has xanthomas or corneal arch, risk factors (hypertension, diabetes mellitus, obesity) or atherosclerotic disease [6].

Cascade screening consists of determining the lipid profile in all first-degree relatives (father, mother and siblings) of patients diagnosed with FH. This technique is justified by the fact that the probability of identifying other carriers of the disease is 50% in first-degree relatives, 25% in second-degree and 12.5% in third-degree relatives [6,7].

For cardiovascular risk stratification, the Framingham score, commonly used for this purpose, should not be used for patients with FH, as it underestimates the real risk. The Simon Broome Register Group proposes to consider patients at high cardiovascular risk if they have any of the following characteristics [6]:

- CAD or established cardiovascular disease;
- Smokers;
- Patients with diabetes mellitus (DM);

- Family history of premature CAD (first- or second-degree relatives with CAD onset before 45 years in males and 55 years in females).

Even without the above risk factors, the patient with FH should be considered a patient at high risk in the long term [6].

FH is still a little-known disease in the pediatric population, and lipid profile measurement as a screening test in patients with no clinical examination alterations is taboo in some cultures, such as in Brazil. Molecular tests performed in clinical research have the role of corroborating clinical suspicions through measurable evidence, adding value to medical routine.

FH has an estimated population prevalence of 1 patient for each group of 500 people, it is a disease that has the potential for early development of coronary artery disease. Atherosclerotic changes in carotid arteries appear already in pediatric age, so that early detection of the disease allows structuring a therapeutic plan that can change its long-term prognosis [6,12].

Although science describes the genetic etiology of FH, about a third of the cases with a positive clinical diagnosis do not present the classic structural alterations in related genes. This fact opens a way to be explored for research on potential origins beyond genetics, not only of FH but of several other diseases. Epigenetics is a very plausible hypothesis in this regard, and whose mechanisms take place in the specific time window of the pediatric care range.

Conclusion

FH is a disease that greatly increases the risk of early cardiovascular events with a potential risk of death. It is important that the disease is considered when surveying the family history of a patient still of pediatric age, and that screening strategies are carried out.

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