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CASE REPORT

Importance of identifying genetic cardiovarscular risk in pediatric patients

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Abstract

Introduction: Familial hypercholesterolemia (FH) is a disease with autosomal dominant inheritance, manifesting in homozygous (HFHo) or heterozygous (HFHe) genotypes. It is characterized by elevated plasma cholesterol concentrations, particularly low-density lipoprotein (LDL) cholesterol levels. It can lead to atherosclerotic plaque formation in the coronary arteries and proximal aorta at an early age, increasing the risk of premature cardiovascular events such as angina and acute myocardial infarction .Diagnosis can be made with two aspects: clinical and genetic. **Case report**: We present the case of an asymptomatic adolescent patient with a relevant family history of cardiovascular disease in the first and second degree of consanguinity, hyperlipidemia of difficult management and early deaths. Given the family history and the importance of ruling out an inherited genetic disease associated with cardiovascular risk, a lipid profile was requested with abnormal results of hyperlipidemia at the expense of plasma LDL. Following these results, a molecular panel of genes associated with hypercholesterolemia was requested, obtaining pathogenic variants in the gene encoding the LDL receptor (*LDLR*) and in the LDL receptor adaptor protein 1 (*LDLRAP1*) gene, both associated with familial hypercholesterolemia. **Discussion and conclusion**: With this result, it is possible to carry out an adequate predictive, preventive, personalized and participatory intervention. A targeted treatment can be established, an adequate follow-up and genetic counseling can be carried out, including risk of heritability, active search for other possible relatives carriers of the disease, and thus have an impact on morbidity and mortality.

INTRODUCTION

Familial Hypercholesterolemia (FH) is a genetic condition with high prevalence in the general population around the world. It is characterized by elevated plasma cholesterol levels, particularly low-density lipoprotein (LDL) cholesterol levels [1]. Individuals affected by FH have an increased risk of early and progressive development of atherosclerotic cardiovascular disease, in children and adolescents, it can be suspected by classic clinical signs, such as tendon xanthomas [2].

The inheritance pattern of FH is autosomal dominant, which can be homozygous (HFHo) or heterozygous (HFHe). The most frequent cause is variants in the gene encoding the LDL receptor (*LDLR*), with less frequent variants in the apolipoprotein B100 (*APOB* 100) gene, in the proprotein convertase subtilisin/kexin 9 (*PCSK9*) gene or in the LDL receptor adaptor protein 1 (*LDLRAP1*) gene [3].

HFHe, has a prevalence of approximately 1 per 312 persons, which translates to an estimated 6.8-8.5 million children and adolescents worldwide [4]. Although nationally there are no official statistics reported, worldwide statistics can be used to estimate that the prevalence of HFHe in Colombia is between 96,000-240,000 [5].

In Colombia, HFHo is one of the recognized orphan diseases [6]. HFHe is not recognized. The Colombian Society of Cardiology and Cardiovascular Surgery convened specialists from

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multiple fields to prepare a review document on HF. Due to the fact that at the national level no actions are undertaken to search for and early diagnosis, and there is no consolidated statistics on the population burden, prevalence and incidence of this pathology, a proposal was made to create a Colombian registry of HF that would allow detailed knowledge of the frequencies and distributions of the forms of HF, a document that is still being drafted [5].

Given the clinical relevance of this pathology, which is considered a public health problem, screening and early detection programs for FH have been created. However, diagnosis at early ages remains a challenge because, in many cases, clinical manifestations at pediatric ages are not observable, or family history is not adequately identified. [7]. The three main features that determine FH are elevated plasma LDL levels, presence of tendinous xanthomas, and a premature onset of atherosclerotic cardiovascular disease [2].

The diagnosis of FH can be made with two aspects: clinical and genetic. Regarding the clinical component, different diagnostic criteria have been described in multiple guidelines and consensus worldwide. Phenotypic diagnosis can be made by stipulating a plasma LDL concentration >190 mg/dL in 2 different blood samples and following a 3-month period of adequate nutrition [8].

The majority of pediatric patients do not show clinical manifestations, however, among them, tendon xanthomas are classic findings, their presence is more indicative of HFHo rather than HFHe [9].

The genetic diagnostic component, is performed by identification of a pathogenic variant, performed with genetic testing [2]. Patients with FH can be classified as monogenic or polygenic. It has been described that monogenic FH is more likely to cause premature coronary events [10].

The management of FH depends on whether it presents with HeFH or HoFH. In the former, lifestyle modifications should be made from diagnosis, then if infants are older than 8 years and LDL is >154 mg/dL it is necessary to initiate statins. Also, if the infant is older than 10 years and LDL is >135 mg/dL, ezetimibe should be added to drug therapy. Whereas, in HFHo, lifestyle changes should be made and both statins and ezetimibe should be initiated together [2]. It is described that if serum LDL values are >135 mg/dL, new and unconventional therapies should be initiated in adults. If they exceed 308 mg/dL, it is suggested to initiate lipoprotein apheresis, and if the latter is not available, the last measure is liver transplantation; in children this therapeutic option has not been described [11].

Currently, several novel drugs are available as treatment options for adults with FH; however, few have been approved for the pediatric population with this disease. On the one hand, it was known that long-lasting inhibition of *PCSK9* synthesis is by inclisiran, a small interfering RNA, can lead to a 47.9% decrease in serum LDL compared to adults with FHHe who received placebo [12]. Its use for the treatment of primary dyslipidemia in adults was approved by the European Medicines Agency (EMA) in 2020, while it is still under evaluation for adult patients with HoFH. Another drug, evolocumab, received US Food and Drug Administration (FDA) approval for patients with HFHo > 12 years of age, and has also demonstrated its potential as a treatment for HFHe children with high serum LDL levels [13].

Also, studies are underway to test the use of alirocumab, an inhibitor of proprotein convertase proprotein convertase subtilisin-kexin (*PCSK9*), in children and adolescents (8-17 years) with HFHe and HFHo, studies that have had promising results [14]. In 2020, FDA-approved bempedoic acid, which reduces blood LDL levels through inhibition of ATP-citrate synthase, was declared alone for the treatment of adult patients with HFHe [15].

Finally, a randomized controlled trial in pediatric patients with HFHo was conducted to evaluate the use of mipomersen as adjuvant therapy, with successful results regarding efficacy parameters in long-term treatment [16]; however, there are no similar trials conducted in children and adolescents with HFHe.

CLINICAL CASE

A 12-year-old male patient, asymptomatic, consulted because of a paternal family history with clinical and paraclinical diagnosis of familial hypercholesterolemia in treatment with statin and biologic therapy, without previous genetic study and 2nd and 3rd degree relatives with a history of dyslipidemia and early death due to heart disease.

Table 1. Sequencing results.

Gene	Variant Coordinates	Amino Acid Change	Zygosis	Clinical Significance	Reference
SMPD1	NM_000543.4: c.688C>T	p.(Arg230)Cys)	Heterozygous	Pathogenic	rs1057516483
SMPD1	NM_000543.4: c.1780_1782del	p.(Thr59del)	Heterozygous	Probably Pathogenic	-

The results showed point variants and copy number variants (CNV) by NGS technology in genes associated with Niemann Pick disease.

On physical examination xanthelasmas, no palpable cutaneous or tendon xanthomas, normal vital signs for age, weight, gender, body mass index between 0 to +1 standard deviation, no hepatomegaly, no corneal alterations. She has lipid profile with total cholesterol levels of 372 mg/dL (normal value <200 mg/dL), HDL cholesterol of 38 mg/dL (normal value >60 mg/dL), LDL cholesterol of 304 mg/dL (normal value <130 mg/dL) and triglycerides of 159 mg/dL (normal value <150 mg/dL).

Given the relevant family history associated with cardiovascular risk of genetic origin without family molecular studies and given the importance of an accurate and specific diagnosis, in order to establish a targeted and personalized treatment, follow-up, prognosis and genetic counseling including risk of heritability, a molecular panel of genes associated with familial hypercholesterolemia was requested using NGS (Next Generation Sequencing) + CNVs (Copy Number Variants) that included the genes (A*BCG5, ABCG8, APOB, LDLR, LDLRAP1, PCSK9*). Pathogenic variants with autosomal dominant heterozygous inheritance pattern were reported in the *LDLR* (Mendelian Inheritance in Man (MIM) *606945) and LDLRAP1 (MIM *605747) genes, which respectively are associated with autosomal dominant familial hypercholesterolemia 1 (MIM #143890) and autosomal recessive familial hypercholesterolemia 4 (MIM #603813).

The molecular panel of genes associated with familial hypercholesterolemia using NGS (Next Generation Sequencing) + CNVs (Copy Number Variants) methodology that included the genes (*ABCG5, ABCG8, APOB, LDLR, LDLRAP1, PCSK9*), reported a pathogenic heterozygous variant in the *LDLR* gene, consisting of the change of a cytosine for a thymine at position 1. 246 of the cDNA, in exon 9/18 of the gene (c.1246 C>T), which at the protein level generates the missense change of an arginine for a tryptophan at codon 416 (p.Arg216Trp), a highly conserved amino acid residue located in the functional domain "LDL-receptor class B1". He also reported a probably pathogenic heterozygous variant in the *LDLRAP1* gene, consisting of a deletion at position 604 of the cDNA corresponding to exon 6/9 (c.604del), which at the protein level produces the frameshift change leading to a premature stop signal at codon 204 (p.Ser202ProfsTer2) in a 309 amino acid protein. Pathogenic variants in the *LDLR* gene (OMIM *606945) are associated with autosomal dominant familial hypercholesterolemia 1 (OMIM #143890). Pathogenic variants in the *LDLRAP1* gene (OMIM *605747) are associated with autosomal recessive familial hypercholesterolemia 4 (MIM #603813), which confers heritability risk. The patient was documented to carry the heterozygous pathogenic variant c-1236C>T; p.Arg416Trp in the *LDLR* gene; the dyslipidemia phenotype being concordant and listed in association with hypercholesterolemia (see Table 1).

This variant is classified as pathogenic given the manifest alteration on the recycling of the defective receptor (ClinVar ID: 357985), which also impacts on the response of patients to the pharmacological use of statins. He also carries the probably heterozygous pathogenic variant c.604del; p.Ser202ProfsTer2 in the *LDLRAP1* gene. This variant probably produces a mRNA transcript degraded by the NMD (nonsense mediated decay) system or a non-functional protein.

Familial hypercholesterolemia (FH) is a disease of autosomal dominant inheritance pattern, which can be homozygous (HFHo) or heterozygous (HFHe), and is characterized by elevated plasma cholesterol concentrations, particularly low-density lipoprotein (LDL) cholesterol levels. It can lead to atherosclerotic plaque formation in the coronary arteries and proximal aorta at an early age, increasing the risk of premature cardiovascular events such as angina and acute myocardial infarction.

The diagnosis of FH can be made with two aspects: clinical and genetic. This patient fulfills both aspects. Regarding the clinical

component, he presents serum LDL levels >160 mg/dl and complies with family history of premature coronary heart disease and diagnosis of hypercholesterolemia in first-degree relative. Molecular diagnosis of familial hypercholesterolemia involves the identification of heterozygous pathogenic variants in the *APOB, LDLR or PCSK9* genes, and as an alternative possibility, biallelic pathogenic variants in the *LDLRAP1* gene can be identified (PMID:24404629). The cholesterol uptake process requires the expression of LDLR and the activity of an adaptor protein for *LDLR (LDLRAP1)*, which is involved in the entry of the receptor into the cell once it has taken up cholesterol [17].

FH can be classified as monogenic or polygenic, which is caused by the association of common genetic variations. It has been described that the FH that is more prone to cause coronary events more prematurely is monogenic [10]. In this patient, a heterozygous pathogenic variant in the *LDLR* gene and a heterozygous probably pathogenic variant in the *LDLRAP1* gene were found. Both are associated with familial hypercholesterolemia of autosomal inheritance, which confers risk of heritability. Interactions in these genes lead to greater severity and early adverse cardiovascular outcomes.

The most frequent cause of FH is variants in the gene encoding LDLR receptors and, less frequently, variants in the *LDLRAP1* gene [3]. HeFH has a prevalence of approximately 1 in 312 persons, which translates into an estimated 6.8-8.5 million children and adolescents worldwide [4]. Although nationally there are no official statistics reported, it can be estimated that the prevalence of HFHe in Colombia is between 96,000-240,000 [5].

In Colombia, there is no protocol or guideline on pediatric population screening for this disease. On the other hand, worldwide, universal screening at birth is not recommended, although it is feasible in the context of neonatal screening for some metabolic diseases; however, this requires governmental support. In Italy, selective screening is recommended between 2 and 10 years of age, since at this age serum lipid values are constant, being similar to those found in early adulthood [18]. In recent years, some authors in developed first world countries recommend cascade screening of children with first and second degree relatives with the disease [19].

Currently, several novel drugs are available as treatment options for adults with FH; however, few have been approved for the pediatric population with this disease. Among the drugs that stand out for pediatric use, evolocumab is described, which received U.S. Food and Drug Administration (FDA) approval for patients with FHo > 12 years of age, and has also demonstrated potential as a treatment for children with high serum LDL levels [13]. Also, studies are underway to test the use of alirocumab, a proprotein convertase subtilisin-kexin (PCSK9) inhibitor, in children and adolescents (8-17 years) with HFHe and HFHo, studies that have had promising results [14]. Due to the family history of first and second degree of consanguinity with death at an early age and history of dyslipidemia, it is necessary to perform a directed pharmacological and non-pharmacological management with this patient, in addition to strict follow-up to prevent premature acute coronary events and adverse outcomes.

CONCLUSIONS

FH is a genetic condition with high prevalence in the general population around the world. It is characterized by elevated plasma cholesterol concentrations, particularly LDL cholesterol levels, which leads to an increased risk of early and progressive development of atherosclerotic cardiovascular disease. The most frequent cause is variants in the gene encoding *LDLR* and, less frequently, variants in the *LDLRAP1* gene.

In Colombia, HFHe is not part of the orphan diseases [6]. Nor is there a publication aimed at the diagnosis and treatment of this disease in any of its inheritance patterns. At the national level, there are no statistics on the prevalence of the disease, much less in pediatrics. A proposal was made to create a Colombian registry of FH that would allow detailed knowledge of the frequencies and distributions of the forms of FH, a document that is still being developed [5]. This study is necessary to know the population burden of this pathology, characterize the patients with this disease, make an early identification through the affected families and thus be able to carry out an adequate follow-up to manage the patients and thus avoid early outcomes that increase morbidity and mortality due to cardiovascular diseases in this population.

Given the clinical relevance of this pathology, which is considered a public health problem, screening and early detection programs for FH have been created. However, diagnosis at an early age remains a challenge because in many cases, in the

pediatric age, there will not be classic clinical manifestations or family history will not be adequately documented [7]. The patient in the reported case was asymptomatic and had no abnormal findings on physical examination.

In Colombia, there are no official statistics reported on the prevalence of this disease. More studies are needed to better address this pathology, increase screening, describe the population burden, raise awareness among health personnel to consider this pathology as a differential diagnosis for good genetic counseling, so that asymptomatic patients can be found and may be at risk of developing early cardiovascular disease and thus avoid them.

It is also necessary to strengthen public health strategies for the promotion and prevention of health in the entire population. Early identification of this disease is a priority through a complete medical history, physical examination, knowledge of family genetic risks and the importance of screening the population, approaching anticipatory, preventive, predictive, participatory and preventive medicine.

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