

Early Cascade Screening and Lipid-Lowering Therapy in Childhood: Challenges in the Management of Familial Hypercholesterolemia

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Abstract

This case highlights the importance of cascade screening for the early diagnosis of Familial Hypercholesterolemia (FH) in children. Early identification at the age of five enabled the timely initiation of lipid-lowering therapy and underscored the need for individualized treatment based on atherosclerotic risk. Despite a substantial reduction in LDL-C levels, the patient remained above recommended therapeutic targets, emphasizing the need for ongoing monitoring and treatment intensification. The detection of subclinical atherosclerosis further reinforces the importance of continuous cardiovascular surveillance. A comprehensive management strategy combining cascade screening, family-based risk assessment, and early intervention is essential to reduce long-term cardiovascular risk and improve clinical outcomes.

Introduction

Familial Hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism characterized by markedly elevated plasma levels of low-density lipoprotein cholesterol (LDL-C), frequently accompanied by clinical manifestations such as tendon xanthomas and corneal arcus.^{1,2}

The clinical phenotype of FH most commonly results from pathogenic variants in the LDLR gene, which encodes the LDL receptor. It may also result from pathogenic variants in the APOB gene, which encodes apolipoprotein B-100 (ApoB-100). Defective ApoB-100 has reduced affinity for the LDL receptor. Alternatively, FH may result from gain-of-function variants in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene, which encodes neural apoptosis-regulated convertase-1 (NARC-1), leading to accelerated LDL receptor catabolism.² Individuals with heterozygous FH retain approximately 50% of normal LDL receptor activity, whereas those with homozygous FH typically have minimal or absent receptor function because both LDLR alleles are affected.¹

Keywords

Hyperlipoproteinemia Type II; Atherosclerosis; LDL Lipoproteins

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Familial hypercholesterolemia is associated with a markedly increased risk of premature atherosclerotic cardiovascular disease. Without early diagnosis and appropriate treatment, affected individuals are at substantially increased risk of cardiovascular complications. FH should be suspected in adults with LDL-C levels >190 mg/dL and in children or adolescents with LDL-C levels >160 mg/dL.³⁻⁵

Early recognition during childhood or adolescence is of utmost importance; after all, it is estimated that a child with FH is born every minute worldwide. Nevertheless, establishing the diagnosis during childhood remains challenging in routine clinical practice.¹

Therefore, this case report, approved by the institutional Ethics Committee (CAAE: 93770325.1.0000.5479), highlights the value of early identification through LDL-C assessment and cascade family screening, enabling the timely initiation of lipid-lowering therapy. Thus, early, individualized management of FH is essential to substantially reduce long-term cardiovascular morbidity and mortality while improving patient prognosis.

Case Report

Male patient, 8 years old, followed at a specialized dyslipidemia outpatient clinic in a public tertiary-care hospital in São Paulo, Brazil. He presents a significant family history of hypercholesterolemia. His maternal grandmother and mother have both been followed at the same clinic since 2022. Their Dutch Lipid Clinic Network Score (DLCNS) values were 5 and 12, corresponding to possible and definite FH, respectively. Due to the unavailability of genetic testing at the institution, the DLCNS was used to guide clinical diagnosis and management, classifying FH as possible (3–5 points), probable (6–8 points), or definite (> 8 points).¹ The patient's maternal grandmother had experienced an acute myocardial infarction at 72 years of age and had bilateral carotid atherosclerotic plaques, as well as enlargement of the aortic arch identified on chest radiography. The patient's 40-year-old mother had corneal arcus and acanthosis nigricans, with a baseline LDL-C concentration of 250 mg/dL. She has been receiving atorvastatin 80 mg/day since 2023, achieving a reduction in LDL-C to 160 mg/dL after two years of follow-up.

Given this family history, the patient underwent cascade screening and was referred to the Dyslipidemia Clinic at 5 years of age. He was classified as having possible FH (DLCNS = 4). Genetic testing was not performed because it was unavailable at our institution. Specialized follow-up was initiated promptly due to the high cardiovascular

risk. At admission, the patient appeared well, with normal perfusion, no respiratory distress, and no fever. No tendon xanthomas or corneal arcus were observed. Cardiac auscultation was unremarkable. He was not taking any medication. Considering the possible introduction of statins, laboratory tests were requested, including total cholesterol (TC), triglycerides, LDL-c, HDL-c, creatinine, fasting glucose, thyroid-stimulating hormone (TSH), urinalysis, creatine aspartate aminotransferase, and alanine aminotransferase.

The patient presented an LDL-C concentration of 249 mg/dL and total cholesterol of 312 mg/dL at 2 years of age. At the initial evaluation in our clinic, at 5 years of age, total cholesterol was 319 mg/dL and LDL-C was 246 mg/dL. At 6 years of age, transthoracic echocardiography revealed a 3-mm calcified hyperechoic nodular lesion located on the inferior aspect of the aortic arch (Figure 1). To further characterize this finding, coronary computed tomography angiography was performed and demonstrated no evidence

of coronary atherosclerosis, with a coronary artery calcium score of zero. Carotid ultrasonography showed normal carotid intima-media thickness and no evidence of atherosclerotic plaque.

Given this clinical picture, atorvastatin 10 mg/day was started at age 5. Because LDL-C remained elevated at 165 mg/dL after 12 months of treatment, the atorvastatin dose was increased to 20 mg/day. The patient currently remains on this regimen. His most recent lipid profile demonstrated total cholesterol of 188 mg/dL and LDL-C of 115 mg/dL. He continues regular follow-up at the specialized outpatient clinic in São Paulo, undergoing semiannual evaluations for monitoring lipid profile, therapeutic efficacy, adverse events, and clinical manifestations.

Discussion

This case highlights the need for systematic cascade screening in families with a significant history of

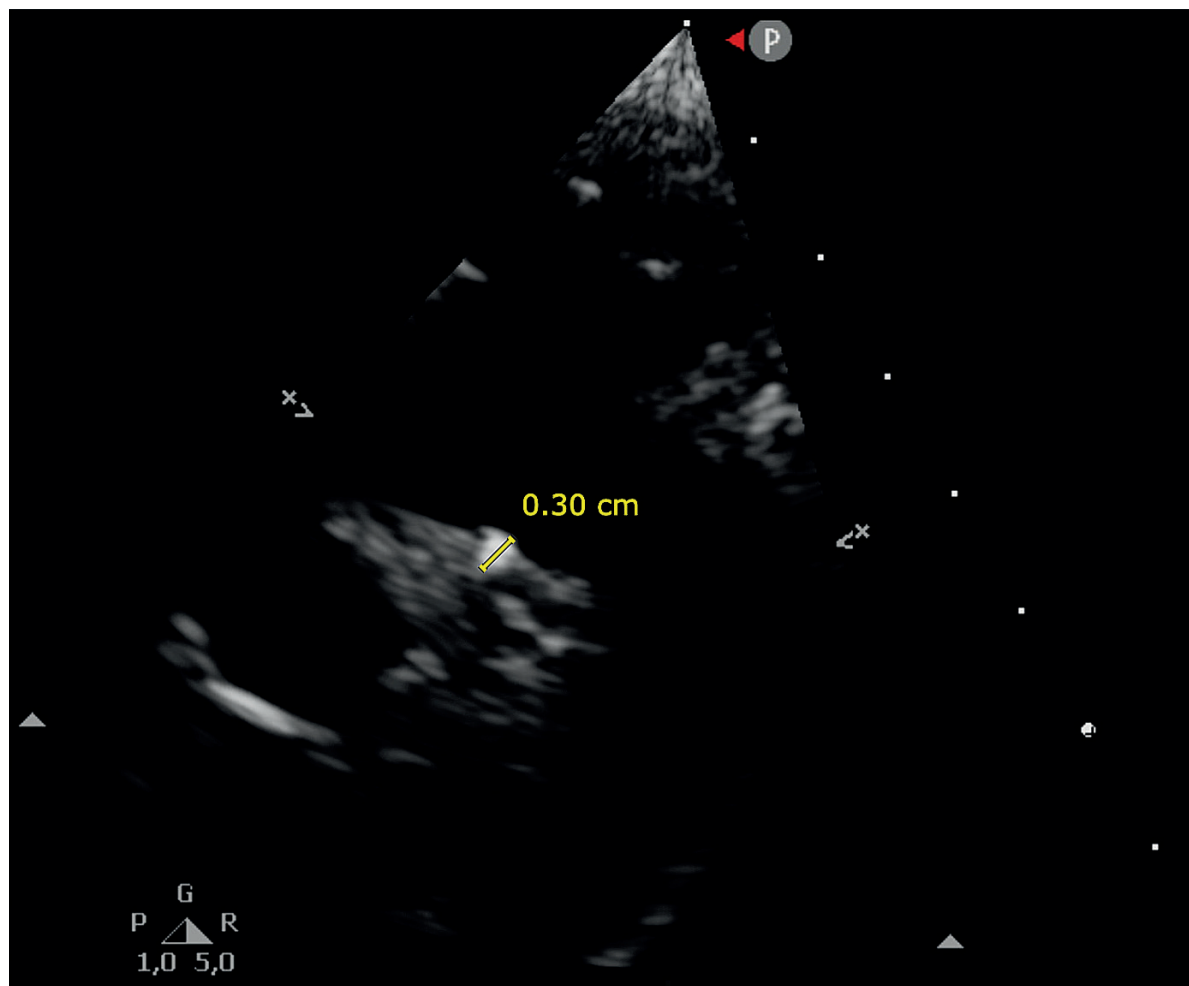


Figure 1 – Echocardiogram showing a calcified, hyperechoic nodular lesion measuring 3 mm on the caudal surface of the aortic arch.

Case Report

hypercholesterolemia and premature atherosclerotic cardiovascular disease. Furthermore, it reinforces the importance of establishing adaptable guidelines for the individualized management of children with FH, thereby ensuring better long-term prognosis and quality of life.

A recent French retrospective study involving 3,232 individuals demonstrated that cascade screening was associated with a 51% reduction in cardiovascular events among patients with genetically confirmed heterozygous FH, most likely due to earlier initiation of treatment.⁶ Although genetic confirmation remains the diagnostic gold standard, its limited availability in Brazil represents an important barrier to the implementation of universal genetic screening. Consequently, alternative diagnostic strategies for FH screening may be useful in outpatient management. However, the DLCNS may be insufficient for diagnosis in the pediatric population, as it was developed for adults and incorporates clinical features that are rarely observed during childhood, such as premature cardiovascular disease, tendon xanthomas, and corneal arcus.⁷

Given this context, the use of lipid-lowering therapy in children with FH is justified due to their increased risk of developing premature atherosclerosis.^{1,2} Although cardiology guidelines recommend the introduction of statins from the age of 8 years,³ with a strong recommendation and moderate certainty of evidence,⁸ the presence of subclinical atherosclerosis in this patient supported the anticipation of therapy, reinforcing the need for individualized clinical management. Growing evidence from the literature suggests that earlier initiation of statin therapy may delay the progression of atherosclerosis and significantly reduce the risk of cardiovascular disease in adulthood, thus justifying the therapeutic approach in this case.

Despite the significant reduction in LDL-c in our patient, levels remain above the ideal targets (< 100 mg/dL for intermediate-risk patients and < 70 mg/dL for those at high cardiovascular risk).^{3,5}

In patients with FH, continuous monitoring and therapeutic intensification are essential, including the consideration of pharmacological combinations with ezetimibe and/or PCSK9 inhibitors in more refractory cases. According to the most recent Brazilian Guideline on Dyslipidemia, ezetimibe may be added from 6 years of age when lipid goals are not achieved, although this recommendation is based on low-certainty evidence. In contrast, PCSK9 inhibitors are recommended for selected patients older than 8 years with persistent severe hypercholesterolemia despite optimized therapy, supported by moderate-certainty evidence and a strong recommendation.⁸ Pharmacological therapy should always be accompanied by comprehensive lifestyle interventions, including adherence to lifestyle modifications, such as a balanced diet and regular physical activity, is crucial to optimize outcomes and prevent early cardiovascular complications. Overall, this

case illustrates that the management of pediatric FH requires a personalized approach integrating cascade screening, careful cardiovascular risk stratification, lifestyle modification, and timely escalation of the established pharmacological therapy.

Conclusion

This case highlights the importance for cardiologists, in general, to carefully consider family history, as it may provide clues of subclinical atherosclerosis in other family members, including children. Cascade stratification for the early identification of FH will allow for a reduction in underdiagnosis, as well as timely initiation of appropriate therapy.

Therefore, an individualized, rigorous, and global risk-based treatment approach is fundamental to reducing the likelihood of premature cardiovascular events.

Author Contributions

Conception and design of the research and critical revision of the manuscript for intellectual content: Alves RJ; acquisition of data and statistical analysis: Zanotti JS; analysis and interpretation of the data: Zanotti JS, Alves RJ; writing of the manuscript: Zanotti JS, Martim ETQ, Alves RJ.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Santa Casa de Misericórdia de São Paulo under the protocol number CAAE 93770325.1.0000.5479. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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