Homozygous Familial Hypercholesterolaemia: A Case Series of LDLR Gene Mutations

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ABSTRACT

Homozygous familial hypercholesterolaemia (HOFH) is characterised by decreased LDL receptor (LDLR) activity reducing the LDL cholesterol's ability to be cleared by the plasma. HOFH is associated with a substantially high risk of death due to cardiovascular problems if left untreated. The treatment involves lipid-lowering drugs and is recommended for all age groups. Two paediatric cases of HOFH are presented in this case series; a five-year male with xanthomas on elbows, knees, and buttocks, and a seven-year male with xanthomas on knees, elbows, and Achilles tendon. Both had elevated lipid profiles, impaired lipoprotein electrophoresis, and LDLR gene mutations, confirming HOFH. Treatment included statins and ezetimibe along with dietary modification and follow-up.

Key Words: *Familial hypercholesterolaemia*, *LDL receptor deficiency*, *Hyperlipoproteinaemia Type II*.

How to cite this article: Noor N, Rai VR, Ibrahim MN, Riaz M, Parveen R. Homozygous Familial Hypercholesterolaemia: A Case Series of LDLR Gene Mutations. *JCPSP Case Rep* 2025; **3**:104-106.

INTRODUCTION

An uncommon autosomal dominant disorder, homozygous familial hypercholesterolaemia (HOFH), is characterised by reduced LDL receptor (LDLR) activity impairing LDL cholesterol's ability to be cleared by the plasma.[1] While heterozygous familial hypercholesterolaemia (HFH) is more common (1 in 200 individuals), HOFH affects only one in one million individuals.[2,3] Early childhood arcus cornealis, high LDL cholesterol levels, tendinous and cutaneous xanthomas, atherosclerosis, and cardiovascular disease (CVD) are common presentations for HOFH patients.[4,5] We present two patients in this case series who were identified as having HOFH based on genetic testing.

CASE 1:

A five-year male presented with small swellings on his elbows and knees for three months. The patient, a twin, had consanguineous parents; his twin and another sibling had similar swellings. One sibling died at six months due to congenital heart disease.

Physical examination revealed yellowish subcutaneous nodules (1 × 1 cm) on elbows and knees, and an ulcerated lesion on the right knee. All lesions were soft and non-tender. His twin brother had similar nodules (Figure 1), and their father had orange-yellow plaques around the eyes.

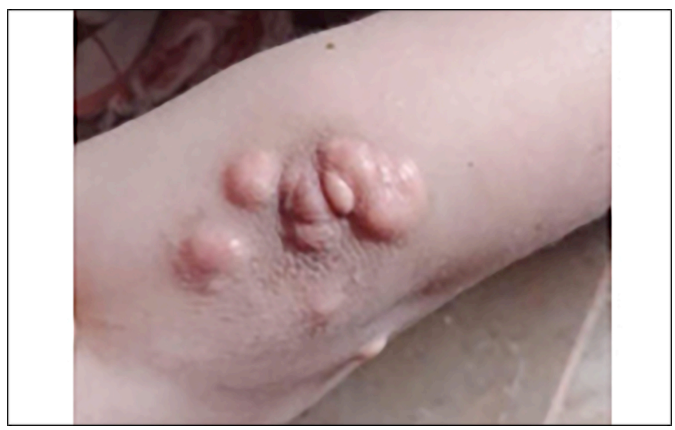

Figure 1: Elbow xanthomas in the brother of the index patient.

The patient showed a normal echocardiogram with normal cardiac valves and no evidence of aortic stenosis. CT angiography was planned which revealed plaque deposition in the right coronary artery causing minimal luminal stenosis. Lipid profile showed elevated cholesterol, triglycerides, LDL, VLDL, and non-HDL cholesterol, with low HDL cholesterol for both the patient and his family members. Lipoprotein electrophoresis revealed borderline elevated beta-lipoprotein levels at 71.1% (normal range: 39-70%) and low alpha lipoprotein levels at 6.6% (normal range: 23-53%), indicating Type IIa HOFH. Genetic analysis identified a homozygous pathogenic variant in the LDLR gene, specifically a mutation in exon 2, disrupting protein production. No evidence of arcus juvenilis, fatty liver disease, or premature coronary artery atherosclerosis was found. The patient was prescribed atorvastatin 5 mg/day, ezetimibe 5 mg/day, dietary advice, and a follow-up in three months. Follow-up after two months revealed improvement in lipid profile.

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Received: July 06, 2024; Revised: November 23, 2024; Accepted: December 01, 2024
DOI: https://doi.org/10.29271/jcpspcr.2025.104

Table I: Lipid profile results of the index patient, his brother, and his father.

Name	Index patient	Brother	Father	Normal range (mg/dl)
Serum cholesterol	787	787	253	≤200
Serum triglycerides	251	215	85	70-150
HDL-cholesterol	16	14	45	≥35
LDL-cholesterol	666	716	191	≤150
VLDL-cholesterol	50	43	17	Upto 40
Non-HDL cholesterol	771	773	208	≤130

CASE 2:

A seven-year male was referred for increasing xanthomas on knees, elbows (Figure 2), and Achilles tendon since the age of three years. The fourth child of consanguineous parents, he had a family history of premature CVD, with two siblings dying at 11 and 9 years of age.

Initial examinations showed total cholesterol at 690 mg/dL (normal range: <200 mg/dL) and beta lipoprotein at 76.1% (normal range: 39-70%). The echo was normal.

Genetic testing confirmed HOFH. DNA sequencing revealed a homozygous mutation in exon 2, causing a premature stop signal (P.Try42) in the LDLR gene, disrupting protein production. This variant is known to be pathogenic and has been observed in individuals with hypercholesterolaemia. The patient was prescribed atorvastatin, 5 mg/day, ezetimibe 5 mg/day, dietary advice, and advised CT angiography on follow-up after three months. Unfortunately, this patient was lost to follow-up and did not return for a second visit; consequently, no further details are available for this case.

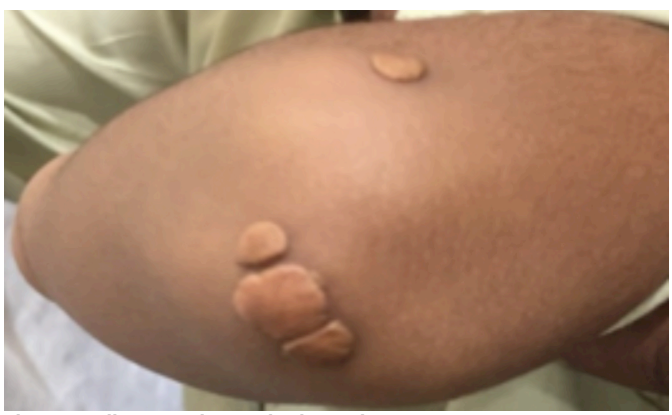

Figure 2: Elbow xanthomas in the patient.

DISCUSSION

HOFH presents a major clinical challenge due to markedly elevated levels of low-density lipoprotein cholesterol (LDL-C) and a high risk of CVD. If left untreated, there is an increased risk of premature cardiovascular events, before the age of 30 years.[6]

The cornerstone of HOFH management includes aggressive lipid-lowering strategies such as high doses of statins combined with ezetimibe. For patients who do not achieve adequate LDL-C reduction, additional treatments such as PCSK9 inhibitors (e.g., evolocumab and alirocumab) and lomitapide are often employed. These therapies can substantially lower LDL-C levels and improve cardiovascular outcomes.[7] An interesting case reported from Bulgaria highlights the efficacy of PCSK9 inhibitors as part of a triple therapy regimen in managing HOFH in children, achieving significant LDL-C reduction and target levels despite statin intolerance. It underscores the need for accessible advanced therapies such as LDL apheresis in resource-limited settings.[8]

LDL apheresis, a procedure that physically removes LDL-C from the bloodstream, is crucial for patients who do not respond adequately to pharmacologic treatments. It can reduce LDL-C levels by 50-75% per session. Regular use of LDL apheresis delays the progression of atherosclerosis and improves survival rates.[9] Additionally, genetic testing is crucial for first and second-degree relatives to identify possible mutations in the LDLR gene.[10] Family members may exhibit variable phenotypes concerning the severity of hypercholesterolaemia, influencing the need for lipid-lowering agents.

In conclusion, this case report emphasises the significance of early detection, prompt management, and genetic evaluation in HOFH patients and their families to prevent premature cardiovascular complications and improve overall patient outcomes.

PATIENTS' CONSENT:

Written informed consent was obtained from the patients' legal guardians for publication of this case report, including relevant clinical details and images. All identifying information has been anonymised to ensure patients' confidentiality.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

NN: Conception, data collection, manuscript drafting, and critical revision.
VRR: Data collection, literature review, and manuscript preparation.
MNI: Supervision and expert guidance.
MR: Data interpretation and manuscript editing.
RP: Literature review, formatting, and final proofreading.
All authors approved the final version of the manuscript to be published.

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