Case Report

When Xanthomas Tell the Story: A Child with De Novo Familial Hypercholesterolemia

Mohnish Darshan[1], Ajay Kumar[1], Pooja Soni[1], Bhavna Dhingra[1*]

[1]*Department of Pediatrics, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India*

Article Info

[*]***Corresponding Author:***
Bhavna Dhingra, MD, DNB
Department of Pediatrics, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India
E-mail: bhavna.pediatrics@aiimsbhopal.edu.in

Keywords

Cutaneous xanthomas, Familial hypercholesterolemia, LDLR mutation, Pediatric dyslipidemia

Abstract

Background: Cutaneous xanthomas in children are uncommon and often overlooked, yet they may represent the earliest visible clue to severe underlying dyslipidemia. Recognising these lesions can be critical for the timely diagnosis of familial hypercholesterolemia (FH), a condition associated with lifelong cardiovascular risk.

Case Presentation: We describe a 9-year-old child presenting with multiple progressively enlarging, yellowish-orange cutaneous swellings over the gluteal region, elbows, and feet. Initially managed surgically elsewhere, these lesions' recurrent nature prompted further evaluation. Histopathology confirmed xanthomas, and lipid profiling revealed extreme hypercholesterolemia with LDL-C of 529 mg/dL. Genetic analysis identified a heterozygous pathogenic splice-site variant in the LDLR gene (c.313+1G>C), establishing the diagnosis of FH. Notably, both parents had normal lipid profiles, suggesting a likely de novo mutation. Initiation of atorvastatin therapy, combined with dietary modification, resulted in a rapid and substantial decline in LDL-C to 120 mg/dL within 1 month.

Conclusion: This case underscores that "skin can signal the heart," with xanthomas serving as early markers of severe dyslipidemia. Even in the absence of family history, FH must be considered. Early laboratory recognition and genetic confirmation enable timely intervention, significantly altering long-term cardiovascular risk.

Introduction

Familial hypercholesterolemia (FH) is an inherited lipid disorder characterised by markedly raised plasma low-density lipoprotein cholesterol (LDL-C) levels from birth. The majority of cases result from mutations in the LDL receptor gene (LDLR), while variants in apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin 9 (PCSK9) are less frequent causes [1,2]. The condition is transmitted in an autosomal dominant pattern, with an estimated prevalence of heterozygous FH ranging from 1 in 200–300 individuals worldwide, and homozygous FH being much rarer (1 in a million) [2,3].

If unrecognised, lifelong exposure to elevated LDL-C accelerates atherosclerosis, conferring a 10- to 20-fold increased risk of premature coronary artery disease (CAD) [1]. While clinical events in heterozygous FH often appear in early adulthood, severe cases and homozygous FH can manifest in childhood with tendon xanthomas, xanthelasma, and even early coronary syndromes [2,4]. Case reports describe coronary artery bypass grafting and angioplasty for children under 10 years of age with homozygous FH, illustrating the aggressive natural course when left untreated [2,5].

Early identification during childhood is therefore essential. Screening based on lipid profile, combined with clinical signs such as cutaneous or tendinous xanthomas, can provide critical diagnostic clues [2].

Despite its clinical importance, FH remains substantially underdiagnosed and undertreated worldwide. In India, recent prevalence studies using Dutch Lipid Clinic Network criteria suggest FH is more common than previously estimated, but awareness remains low [3]. This gap in recognition delays intervention and leads to preventable cardiovascular morbidity. In this report, we present the case of a 12-year-old child with genetically confirmed heterozygous FH due to a de novo LDLR splice-site mutation, who presented with multiple cutaneous xanthomas and severe dyslipidemia. The absence of family history, incidental detection of additional heterozygous variants, and an excellent early response to statin therapy make this case distinct. It highlights the importance of recognising subtle cutaneous markers in childhood and stresses the need for early treatment and lifelong follow-up to avert premature atherosclerotic disease.

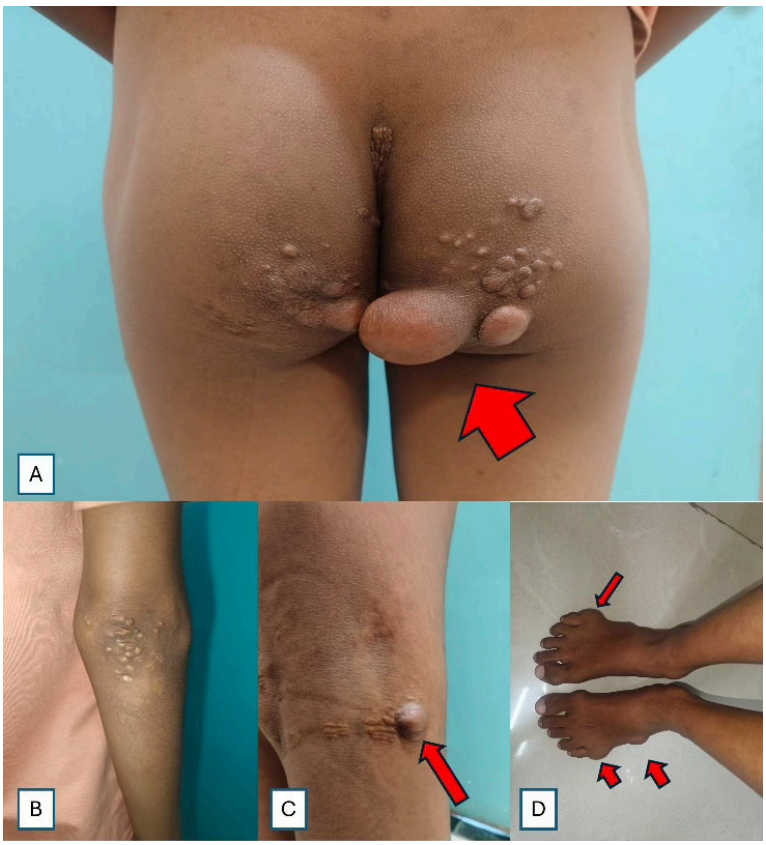
Case description

A 9-year-old child presented with multiple progressively enlarging swellings over the gluteal region for the past six months. The swellings were initially small and gradually increased in size, appearing yellowish-orange and associated with pain on walking and lying supine. The gluteal lesions were the most prominent, with the largest measuring approximately pear-sized (5 x 4 cm), soft in consistency, and smooth, without overlying skin changes or discharge. Over subsequent months, additional swellings developed over both elbows and along the dorsum and lateral borders of both feet. The elbow lesions were smaller, approximately peanut-sized (2 x 1 cm), soft, smooth, and non-tender, with no erythema, ulceration, or discharge. Some of the lesions became tender, and the child experienced significant discomfort. The patient had previously undergone multiple surgical excisions elsewhere for symptomatic relief, but the swellings recurred. No histopathological evaluation had been performed during those interventions.

The child was the fourth-born to non-consanguineous parents, with no family history of coronary heart disease, hypertension or similar skin lesions or. Birth and developmental history were unremarkable. The child was attending school with good scholastic performance. There was no history of systemic illness, drug intake, or chronic comorbidities, preceding trauma or vaccination at the site

On general examination, the child's vitals were within normal limits, and there was no pallor, icterus, cyanosis, clubbing, lymphadenopathy, or pedal oedema. Systemic examination was unremarkable. Local examination revealed multiple globular lesions over the buttocks arising from the dermis and subcutaneous tissue. The largest gluteal lesion measured approximately 5 × 4 cm, was mobile, pedunculated, soft in consistency, and had pinchable overlying skin without fluctuation or discharge. A few lesions showed mild surface abrasions with tenderness. Similar sessile lesions were noted over both elbows, with the largest measuring approximately 2 × 1 cm, soft, smooth, and non-tender, with no overlying skin changes. Examination of the feet revealed soft swellings along the lateral borders, the largest measuring 4 × 3 cm, with pinchable overlying skin, clinically resembling lipomatous lesions (Figure 1).

Figure 1: Clinical photographs showing multiple cutaneous xanthomas in a 9-year-old boy with genetically confirmed familial hypercholesterolemia.



(A) Large, globular, reddish-orange, pedunculated and sessile xanthomas over the gluteal region.

(B) Multiple sessile xanthomas over the extensor surface of the elbow.

(C) Solitary nodular lesion over the lateral aspect of the knee.

(D) Soft xanthomatous swellings along the dorsum and lateral borders of both feet (arrows).

Excision of a buttock lesion was performed, and histopathology revealed foamy macrophages within a fibrous stroma, confirming the diagnosis of xanthoma. Laboratory evaluation revealed normal complete blood counts, renal and liver function tests, and electrolyte levels. Laboratory investigations demonstrated severe dyslipidaemia with total cholesterol 647.6 mg/dL, triglycerides 76.7 mg/dL, HDL 102.8 mg/dL, and markedly elevated directly measured LDL 529.4 mg/dL. Ophthalmological evaluation did not reveal lipemia retinalis or corneal arcus.

Whole Exome Sequencing (WES) identified a heterozygous pathogenic splice-site variant in the LDLR gene (c.313+1G>C, intron 3), classified as pathogenic by ACMG criteria. This mutation disrupts the canonical donor splice site, leading to abnormal RNA splicing and loss of LDL receptor function, thereby explaining the severely elevated LDL-cholesterol levels and cutaneous xanthomas. The condition was confirmed as familial hypercholesterolemia type 1 (FHCL1; OMIM #143890). Parental lipid profiles were within normal limits, suggesting a de novo pathogenic variant; however, segregation analysis was not undertaken due to financial constraints to confirm de novo nature.

Whole exome sequencing also identified the child as a heterozygous carrier for two unrelated pathogenic variants: ABCA4 (c.5882G>A; p.Gly1961Glu), associated with Stargardt disease, and GJB2 (c.71G>A; p.Trp24*), associated with autosomal recessive nonsyndromic hearing loss. These findings are not expected to be clinically expressed in the heterozygous state due to autosomal recessive nature. Comprehensive genetic counselling was provided, addressing the implications of the LDLR variant, the possibility of mosaicism, and the incidental carrier findings.

The child was commenced on atorvastatin therapy (10mg/day) with dietary modification, and screening for cardiovascular end-organ involvement was undertaken. After one month of treatment, there was a marked improvement in the lipid profile, with serum cholesterol 189 mg/dL, triglycerides 109 mg/dL, LDL-C 120 mg/dL, and VLDL-C 21 mg/dL (Table 1).

Table 1: Lipid profile of the patient before and after initiation of atorvastatin therapy compared with normal reference ranges.

Parameters	Before atorvastatin	After atorvastatin	Normal range (mg/dL)
Cholesterol	647	189	<200
Triglycerides	76	109	<150
LDL-C	529	120	<100
VLDL-C	15.35	21	5–40
HDL	102	46	>40

Marked improvement in serum cholesterol and LDL-C (directly measured) was observed after one month of therapy.

Staged surgical excision of the residual xanthomas was planned for cosmetic correction, and the patient was advised long-term follow-up with periodic lipid monitoring, cardiovascular surveillance, ophthalmology and hearing follow-up, along with genetic counselling for the family.

Discussion

Familial hypercholesterolemia (FH) is one of the most common monogenic disorders of lipid metabolism, yet it remains under-recognised in the pediatric population. The hallmark of the disease is a persistently elevated LDL-cholesterol concentration due to pathogenic variants affecting the LDL receptor pathway [7]. The cumulative burden of high LDL from early childhood accelerates atherosclerotic changes and significantly increases the risk of premature coronary artery disease if untreated [2,8]. The presence of cutaneous or tendinous xanthomas in a child should always prompt evaluation for lipid disorders. In our patient, multiple xanthomatous swellings over the buttocks, elbows, and feet were the first clinical clues. Similar observations have been reported in other paediatric cases where tuberous or diffuse xanthomas were the presenting signs of FH [4,6]. Unfortunately, as in this case, repeated surgical excision without histopathological evaluation delayed the diagnosis. Early recognition is crucial because initiation of therapy during childhood reduces lifelong LDL exposure and improves cardiovascular prognosis [7].

Genetic testing has become central to the diagnosis of FH. Whole exome sequencing in our patient revealed a heterozygous splice-site mutation in LDLR (c.313+1G>C). Most reported paediatric FH cases involve inherited variants, either heterozygous or compound heterozygous. An unusual feature in our case was the apparent de novo occurrence of the mutation, as neither parent had a standard lipid profile. While rare, de novo mutations have been described and underline the need to consider FH even in the absence of family history [8]. Molecular confirmation not only establishes the diagnosis but also facilitates cascade screening, reproductive counselling, and individualised management strategies [7,8].
Another distinctive aspect was the incidental detection of pathogenic variants in ABCA4 (linked to Stargardt disease) and GJB2 (linked to recessive non-syndromic hearing loss). Such findings have not been commonly reported in pediatric FH cases and are clinically silent in the heterozygous state, but they broaden the genetic counselling considerations in this family.

Statins remain the first-line therapy for children with FH, with guidelines recommending initiation from 8–10 years of age if LDL-C remains ≥180 mg/dL. In our patient, atorvastatin led to a marked reduction in LDL-C within one month, consistent with the favourable responses observed in other pediatric case series. Early pharmacological treatment is supported by evidence that lipid-lowering therapy in childhood slows progression of subclinical atherosclerosis, as demonstrated by reduced carotid intima–media thickness [7,8].
Monitoring must be comprehensive and ongoing. Lipid profiles should be checked regularly, along with liver and muscle enzyme assays, to ensure the drug's safety. Non-invasive assessments such as echocardiography and carotid Doppler can detect early vascular changes. Longitudinal follow-up is essential, as highlighted by reports of children with homozygous FH developing severe coronary disease as early as the first decade of life [2].

Conclusion

This case and those previously reported share important lessons. First, childhood xanthomas are never trivial and should raise suspicion of FH. Second, genetic testing provides diagnostic certainty, even in sporadic cases without family history. Third, early statin therapy is both safe and effective in children, reducing LDL burden and improving outcomes. Finally, structured monitoring and cardiovascular surveillance are mandatory, as illustrated by cases where delayed treatment led to premature acute coronary events.

Author's Disclosures

Declaration of Conflict of Interests

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Ethical Approval

This study was conducted in accordance with the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki. Ethical approval for the publication of this case report was obtained from the Institutional Ethics Committee. Written informed consent for publication was obtained from the patient's parents/legal guardians.

Credit Author Statement

All authors contributed equally to the writing, development,and finalization of the case report..
All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability Statement

All data supporting the findings of this study are included within the article. Additional clinical details are available from the corresponding author upon reasonable request, subject to institutional and ethical considerations.

Acknowledgements

The authors thank the patient's family for their cooperation and consent for publication of this case report.

References

1. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S1-S8. doi: 10.1016/j.jacl.2011.04.003. Epub 2011 Apr 12. PMID: 21600525.
2. Wang N, Wei Y, Zhou G, Zhang Y, Song J. Acute coronary syndrome in an 8-year-old child with familial hypercholesterolemia: a case report. Journal of Medical Case Reports. 2022;16(1):290. doi:10.1186/s13256-022-03488-3
3. Barde AK, Sethi S, Bhargav M, Waghdhare S. Indian prevalence of familial hypercholesterolemia demystified by applying Dutch lipid clinic network criteria. Int J Adv Med 2022;9:1177-1182.
4. Rahman A, Ahmed MU, Islam AKMM, Karim A, Sarker SA. A young male with familial hypercholesterolemia. J Saudi Heart Assoc. 2012;24(4):261–264. doi:10.1016/j.jsha.2012.06.264 PubMed PMID: 24174835; PubMed Central PMCID: PMC3809505.
5. Chaubal G, Pakkala AK, Nanavati AJ, Hatimi H, Sinha R, Verma L, et al. Compound Heterozygous Familial Hypercholesterolemia in a Child: Successfully Treated by Liver Transplant from Heterozygous Living Donor. Indian Pediatrics Case Reports. 2023;3(4):220. doi:10.4103/ipcares.ipcares_29_23
6. Sinha R, Singh S, Syed VS. Tuberous xanthoma in type 1 familial hypercholesterolemia. Int J Contemp Pediatr 2024;11:1317-1319.
7. Ziółkowska S, Kijek N, Zendran I, Szuster E, Barg E. Familial hypercholesterolemia – treatment update in children, systematic review. Pediatr Endocrinol Diabetes Metab. 2022;28(2):152–161. doi:10.5114/pedm.2022.116112 PubMed PMID: 35848473; PubMed Central PMCID: PMC10214937.
8. Harada-Shiba M, Ohtake A, Sugiyama D, Tada H, Dobashi K, Matsuki K, et al. Guidelines for the Diagnosis and Treatment of Pediatric Familial Hypercholesterolemia 2022. J Atheroscler Thromb. 2023;30(5):531–557. doi:10.5551/jat.CR006 PubMed PMID: 36682777; PubMed Central PMCID: PMC10164603.

Copyright© 1999–2026 International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). All rights reserved.

This is a Platinum Open Access Journal distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.