International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Multiple Cutaneous Xanthomas Revealing Severe Familial Hypercholesterolemia in A Child: A Case Report

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Abstract
Familial hypercholesterolemia (FH) is an inherited disorder characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) from childhood and an increased risk of premature atherosclerotic cardiovascular disease. We report a 12-year-old boy with multiple cutaneous and tendinous xanthomas, bilateral xanthelasma, and corneal arcus, with an LDL-C level of 600 mg/dL (15.5 mmol/L). Secondary causes of hypercholesterolemia were excluded. A limited molecular analysis targeting exon 6 of LDLR did not identify a pathogenic variant, while comprehensive genetic testing was unavailable; therefore, the diagnosis remained phenotypic rather than molecularly confirmed. Stepwise atorvastatin titration up to 20 mg/day followed by ezetimibe 10 mg/day reduced LDL-C to 400 mg/dL (10.3 mmol/L), but substantial hypercholesterolemia persisted. This case illustrates the diagnostic and therapeutic challenges of severe pediatric FH when comprehensive genetic testing and advanced lipid-lowering therapies are not readily accessible.

Keywords: Familial hypercholesterolemia; child; xanthomas; LDL-C; statin; ezetimibe.

INTRODUCTION

Familial hypercholesterolemia is one of the most common inherited disorders of lipid metabolism. It is characterized by a persistent elevation of low-density lipoprotein cholesterol (LDL-C) levels due to pathogenic variants primarily in the LDLR, APOB, PCSK9 or LDLRAP1 genes (1,3). Heterozygous familial hypercholesterolaemia (HeFH) is thought to affect around 1 in 250 of the population. The homozygous form (HoFH) is much rarer and more severe, affecting approximately 1 in 300,000-400,000 (1,2).In addition , Lifelong exposure to elevated LDL-C from birth accelerates atherosclerosis and markedly increases the risk of premature cardiovascular disease, particularly in severe forms (1,2). Therefore diagnosis is based on elevated LDL-C levels, suggestive clinical manifestations, family history, and, whenever possible, genetic confirmation (1,3). Tendinous or tuberous xanthomas, xanthelasma and corneal arcus are strongly suggestive of severe FH in children, particularly when associated with very high concentrations of LDL-C (1, 2). .Early management combining the CHILD-2 diet with lipid-lowering therapy—including statins, ezetimibe, PCSK9 inhibitors, or LDL apheresis in the most severe cases—reduces cumulative LDL-C exposure and improves long-term cardiovascular outcomes (1,2,7,8).
We report the case of a 12 year old boy presenting with multiple cutaneous xanthomas revealing severe

familial hypercholesterolemia. Despite progressive statin dose , LDL-C remained markedly elevated, requiring the addition of ezetimibe and further genetic investigations. In the absence of comprehensive genetic testing, the diagnosis remained phenotypic rather than molecularly confirmed. Therfore our case highlights the difficulty in diagnosing severe pediatric FH in the absence of molecular confirmation, and the need for early diagnosis, extensive genetic testing and aggressive lipid-lowering therapy to minimize long-term cardiovascular risk.

Case Presentation

A 12-year-old boy had been followed since the age of 10 years for severe hypercholesterolemia revealed by multiple xanthomas. He was born to non-consanguineous parents. Parental lipid screening showed an LDL-C level of 101 mg/dL (2.61 mmol/L) in the father and 89 mg/dL (2.30 mmol/L) in the mother. Apart from the parents, the remaining family members had not undergone lipid screening. His siblings were clinically asymptomatic, and no other family member was reported to have similar clinical manifestations. Notably ,his symptoms began at the age of 5 years with the gradual appearance of yellowish cutaneous lesions over the buttocks, leading to hospitalization at the age of 10 years for evaluation.

Also, he was not receiving medications known to induce secondary dyslipidemia; corticosteroids, retinoids, immunosuppressive agents, antiretroviral drugs, or atypical antipsychotics. On admission, he was in good general condition. His weight was 36 kg (−1 SD) and his height 1.50 m (−0.5 SD). Cardiovascular examination revealed a heart rate of 70 beats/min, blood pressure of 110/65 mmHg, within the normal range for age, no cardiac murmur, normal peripheral pulses, a normal electrocardiogram, with no signs of heart failure, dyspnea, or angina. Abdominal examination was normal , with no hepatosplenomegaly.

Dermatological examination revealed bilateral tuberous xanthomas over the knees, tendinous xanthomas involving the metacarpophalangeal joints, extensive xanthomas over the dorsal buttocks, bilateral upper eyelid xanthelasma, and corneal arcus (Figure 1). No eruptive, palmar, or tuberoeruptive xanthomas were observed. The remainder of the physical examination was unremarkable.

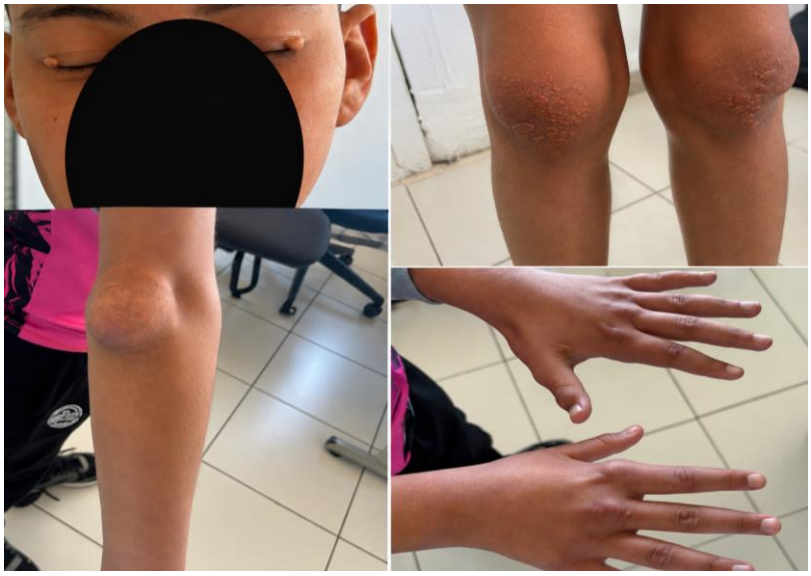

Figure 1. Clinical photographs illustrating bilateral xanthelasma of the upper eyelids and multiple tuberous and tendinous xanthomas involving the dorsal hands, elbows, and knees. Facial features have been partially masked to preserve patient anonymity

Moreover laboratory investigations showed severe isolated hypercholesterolemia, with a total cholesterol of 700 mg/dL (18.1 mmol/L) and an LDL-cholesterol of 600 mg/dL (15.5 mmol/L), triglycerides 53 mg/dL (0.60 mmol/L) and HDL-cholesterol 50 mg/dL (1.29 mmol/L) were normal. Also , The initial workup showed no evidence of secondary dyslipidemia. Fasting plasma glucose, HbA1c, thyroid and renal function, urine protein analysis, serum protein electrophoresis, liver enzymes, bilirubin, and creatine phosphokinase (CPK) were all within normal limits.

Therefore , the early onset of xanthomas and markedly elevated LDL-cholesterol strongly suggested severe familial hypercholesterolemia. The main differential diagnoses included homozygous FH (HoFH), severe heterozygous FH (HeFH), and compound heterozygous FH (cHeFH). A limited molecular analysis targeting exon 6 of LDLR did not identify a pathogenic variant. However, comprehensive sequencing of LDLR and other FH-associated genes, together with copy-number variant analysis, was not available.

In addition cardiovascular assessment revealed a left ventricular ejection fraction of 65%, mild right ventricular dilatation, trivial aortic regurgitation, thickening of the aortic valve suggestive of lipid deposition, and mild narrowing of the aortic root and ascending aorta, without visible coronary abnormalities. No systemic hypertension was documented.

In the present case, lifestyle and dietary interventions were initiated together with atorvastatin, starting at 5 mg/day and gradually increased to 20 mg/day. Despite increasing atorvastatine, LDL-cholesterol remained around 600 mg/dL (15.5 mmol/L). Ezetimibe 10 mg/day was therefore added at the age of 12 years reducing LDL-cholesterol from 600 mg/dL (15.5 mmol/L) to 400 mg/dL (10.3 mmol/L) after one month. The treatment was initially introduced with a stepwise statin titration. In retrospect, given the severity of the phenotype, current HoFH recommendations would favor upfront combination therapy with a high-intensity statin and ezetimibe, followed by rapid therapeutic escalation (11). Nevertheless, LDL-C remained well above the recommended therapeutic target of ≤115 mg/dL (≤3.0 mmol/L) according to the 2026 EAS pediatric recommendations (11), supporting the diagnosis of a severe form of familial hypercholesterolemia and justifying further genetic investigations and consideration of second-line lipid-lowering therapies. (Figure 2).

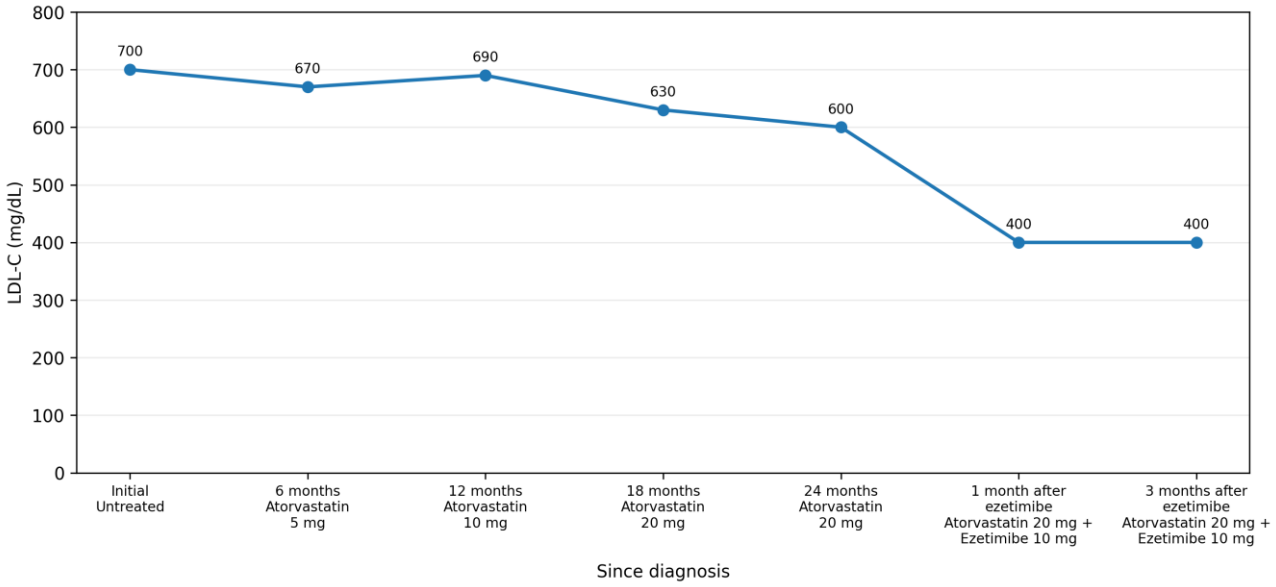

Figure 2. Evolution of LDL-cholesterol during therapeutic follow-up.

Discussion

Familial hypercholesterolemia is a genetic disorder with high low-density lipoprotein cholesterol (LDL-C) from birth, leading to accelerated atherosclerosis and an increased risk of premature cardiovascular disease (1). In addition, children early diagnosis is essential to reduce cumulative LDL-C exposure and prevent long-term cardiovascular complications (1,2).

The clinical presentation of our patient strongly suggests a severe form of FH. The early onset of tendinous and tuberous xanthomas, corneal arcus, and an LDL-C level of 600 mg/dL (15.5 mmol/L) is highly suggestive of homozygous familial hypercholesterolemia (HoFH) or compound heterozygous familial hypercholesterolemia (cHeFH), as reported in recent pediatric studies (4,6). The limited molecular analysis targeting exon 6 of LDLR did not identify a pathogenic variant and does not exclude the diagnosis, since pathogenic variants may involve other regions of LDLR or other genes implicated in LDL metabolism (2,3). Also , The latest guidelines support next generation sequencing (NGS) panels including ; LDLR, APOB, PCSK9, and LDLRAP1 (2,3,6).

Moreover secondary causes of hypercholesterolemia must be excluded including ; hypothyroidism, nephrotic syndrome, cholestatic liver disease, metabolic disorders, obesity, and drug-induced dyslipidemia (2). In our patient, markedly elevated LDL-C associated with normal triglyceride levels and multiple xanthomas strongly supported a genetic etiology. The workup for secondary hypercholesterolemia was unremarkable. Although apolipoprotein B and lipoprotein(a) measurements would have refined cardiovascular risk assessment, they could not be performed because of financial constraints (2,3).

Importantly , management of FH combines lifestyle and dietary interventions based on the CHILD-2 diet, limiting saturated fat intake to <7% of total energy intake and dietary cholesterol to <200 mg/day, together with intensive lipid-lowering therapy (1,2). Statins are the first-line treatment in children. Furthermore , pravastatin is approved from 8 years of age, whereas atorvastatin, rosuvastatin, simvastatin, lovastatin, and fluvastatin are approved from 10 years (9). Treatment should start at the lowest effective dose and be progressively titrated according to LDL-C levels, with regular monitoring of the lipid profile, liver enzymes, and CPK in patients with muscle symptoms (2,7). Statins have consistently been shown to slow atherosclerosis progression and reduce long-term cardiovascular risk in childre with FH (1,2,7).

In cases of an insufficient response to statin monotherapy, **Iughetti et al.** (9) recommend adding **ezetimibe** to achieve further LDL-C reduction through statin–ezetimibe combination therapy (2,9).
In our patient, despite adherence to a CHILD-2 diet and gradual up-titration of atorvastatin to 20 mg/day, LDL-C remained markedly elevated. The addition of ezetimibe resulted in a partial LDL-C reduction but did not achieve adequate LDL-C control. Furthermore when LDL-C remains inadequately controlled despite optimal statin–ezetimibe therapy, PCSK9 inhibitors may be considered. Evolocumab is approved from 10 years of age, whereas alirocumab is approved from 8 years of age for children with HeFH (11). Therefore, our patient met the criteria for PCSK9 inhibitor therapy. However, treatment could not be initiated because these agents are unavailable in Morocco and unaffordable for the family abroad. Surgical excision of xanthomas is not an alternative to lipid-lowering therapy and should be reserved for significant functional or cosmetic impairment after sustained lipid control because of the high risk of recurrence, particularly for tendinous xanthomas (2).
In term of follow-up, Johansen et al. emphasize the need for lifelong clinical, biochemical, and cardiovascular monitoring. The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommends regular lipid profile assessment, liver enzyme monitoring after statin initiation or dose escalation, and creatine phosphokinase (CPK) measurement in patients with muscle symptoms (9). Also , Capra et al. stress the importance of adherence to lifestyle and dietary measures, whereas Mainieri et al. recommend periodic cardiovascular evaluation to detect early atherosclerosis and valvular or aortic involvement in severe FH (1,8). Accordingly, our patient will undergo close clinical and biological follow-up with regular lipid profile and liver enzyme assessments, treatment tolerance monitoring, and serial echocardiography. Therapy will be reassessed at each visit, and PCSK9 inhibitor therapy will be considered if it becomes available.

Limitations

In this case, we had several limitations. First, comprehensive genetic testing was unavailable, precluding molecular confirmation and precise characterization of the underlying genotype. Second, apolipoprotein B and lipoprotein(a) levels could not be measured. Finally, access to advanced lipid-lowering therapies and lipoprotein apheresis was limited.
In conclusion, our case highlights the severity of familial hypercholesterolemia, as illustrated by extensive cutaneous xanthomas occurring from early childhood. Also , It emphasizes the importance of long-term multidisciplinary follow-up, particularly regular cardiovascular monitoring, given the high risk of premature atherosclerotic complications. Finally, comprehensive genetic testing remains essential to confirm the diagnosis, guide management, and facilitate appropriate family evaluation.

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