

## CASE REPORT

## Familial hypercholesterolemia presenting with multiple nodules of the hands and elbow

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### Introduction

Familial hypercholesterolemia (FH) is a genetic disease resulting in elevated low-density lipoprotein cholesterol (LDL-C) levels. Most individuals inherit a mutation from one parent, resulting in the heterozygous form heterozygous familial hypercholesterolemia (HeFH). HeFH affects 1 in 500 people, making it one of the most common genetic diseases, yet continues to be underrecognized with <1% of cases diagnosed in many countries, including both developed and developing nations [1–3]. Without treatment, individuals with FH are about 20 times more likely to develop premature coronary heart disease [4]. To the best of our knowledge, this is the first report of HeFH in the English-speaking Caribbean.

### Case Presentation

A 41-year-old man of Portuguese ancestry presented with a chief complaint of cosmetically distressing nodules affecting both hands and the right elbow. These were slowly increasing in size for several years with no history of tenderness, joint stiffness, or trauma and reminded him of nodules on the hands of his maternal uncle. He was in good general health with no comorbidities, smoking, or drug use. Family

### Key Clinical Message

Familial hypercholesterolemia (FH) is a common but commonly missed diagnosis. Tendon xanthomas are a physical sign strongly suggestive of FH. Physicians must identify tendon xanthomas, apply validated clinical scoring such as the Dutch Lipid Clinic Network criteria and offer cascade screening. This approach will increase recognition of FH.

### Keywords

Caribbean, cascade screening, diagnosis, familial hypercholesterolemia, xanthoma.

history revealed a sister who had a myocardial infarction at 45 years of age and was on treatment with several lipid-lowering medications.

Examination showed a normotensive male with a body mass index of 32 kg/m<sup>2</sup>. Inspection and palpation of the hands and elbow demonstrated multiple tendon xanthomas (Figs. 1 and 2). Closer inspection revealed arcus cornealis and thickened Achilles tendons (Figs. 3 and 4).

Laboratory testing was significant for fasting total cholesterol of 403 mg/dL, LDL-C of 347 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 35 mg/dL and normal triglyceride level. Other investigations including electrocardiogram, chest radiograph, and echocardiography were unremarkable.

Given these findings, the Dutch Lipid Clinic Network criteria (Table 1) were applied. This diagnostic scoring of our patient was positive for family history, tendon xanthomas, arcus cornealis in a patient <45 years and LDL-C levels >330 mg/dL. With a total score of 19 points the diagnosis of definite HeFH was made. Diagnosis could also have been made using similar validated clinical criteria developed by the Simon Broome Register Group [5]. As noted by the National Lipid Association Expert Panel on FH, genetic screening is generally not needed and up to 20% of clinically definite FH patients have no identifiable mutation, so a negative genetic test does not exclude FH [4].



**Figure 1.** Multiple tendon xanthomas are seen affecting the extensor tendons of the hands.



**Figure 2.** Prominent xanthoma seen at elbow.



**Figure 3.** Corneal arcus in a patient <45 years should prompt evaluation for hyperlipidemia.



**Figure 4.** Thickened, xanthomatous Achilles tendons are subtle findings that can be better detected by careful palpation in addition to visual inspection.

**Differential diagnosis**

Major differentials for FH include familial combined hyperlipidemia and polygenic hypercholesterolemia. Xanthomas are not seen in polygenic hypercholesterolemia, while in familial combined hyperlipidemia triglyceride levels are generally elevated. Xanthomas can occur in sitosterolemia and cerebrotendinous xanthomatosis, but these have other manifestations and do not involve LDL metabolism [2].

**Treatment and outcome**

Lipid-lowering therapy was initiated with dietary and lifestyle modifications and a statin. On follow-up visits, statin therapy was increased to maximum dose with biochemical monitoring of liver function, but LDL-C concentration remained greater than 50% from baseline. Ezetimibe coadministration was commenced, which resulted in a favorable LDL-C reduction. In keeping with guidelines, cascade screening was offered to the family and the patient’s sister was diagnosed with HeFH. The MEDPED (Make Early Diagnosis-Prevent Early Death)

**Table 1.** The Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolemia.

Criteria	Points
1. Family history: a first-degree relative with known	
a) Premature (age <55 in men, <60 in women) coronary and vascular disease	1
b) Plasma LDL-C concentration >95th percentile for age and sex	
I) In an adult relative	1
II) In a relative <18 years of age	2
c) Tendon xanthomata and/or arcus cornealis	2
2. Clinical history: patient has premature (age <55 in men, <60 in women)	
a) Coronary artery disease	2
b) Cerebral or peripheral vascular disease	1
3. Physical examination	
a) Tendon xanthomata	6
b) Arcus cornealis in a patient <45 years of age	4
4. Laboratory analysis	
a) LDL-C levels >330 mg/dL	8
b) LDL-C levels 250–329 mg/dL	5
c) LDL-C levels 190–249 mg/dL	3
d) LDL-C levels 155–189 mg/dL	1
5. DNA analysis showing a functional mutation in the <i>LDLR</i> gene	8
	Diagnosis (total points)
	Definite HeFH >8
	Probable HeFH 6–8
	Possible HeFH 3–5

Source: World Health Organization [1].

study criteria, which define cut-off LDL-C values based on age and degree of relation, were used for this purpose [4]. At 1-year postdiagnosis the patient continued to do well with no evidence of premature cardiovascular disease or progression of the tendon xanthomas.

## Discussion

Heterozygous familial hypercholesterolemia occurs most commonly due to a mutation of the LDL receptor gene, the discovery for which Goldstein and Brown received the Nobel Prize in Medicine. FH is one of the few genetic disorders which meet all of the World Health Organization criteria for large-scale screening [1]. Despite this, FH is underdiagnosed by cardiologists and general practitioners [6] and as in the case of this patient's sister, sometimes remains undetected even after myocardial infarction [7].

This case report highlights FH in the Caribbean region, where at present no systematic approaches to identify patients with FH and offer cascade screening to their relatives exist. Premature cardiovascular disease exerts a

heavy burden on the region and it is likely that FH represents a significant cause of preventable disease. It has been shown that patients with FH have abnormal arterial structure and function but this can be improved with intensive statin therapy [8]. Therefore, this life-threatening disease is treatable once identified.

Among FH patients, xanthomas have been independently associated with greater cardiovascular risk [9]. Physicians, including general practitioners, cardiologists, and pediatricians, must identify xanthomas during physical examination and utilize validated clinical scoring such as the Dutch Lipid Clinic Network criteria (Table 1). FH is autosomal codominant so it is essential to offer cascade screening to first-degree relatives of diagnosed HeFH patients who are at high risk as demonstrated in the case presented. Implementation of cascade screening will identify many currently unknown cases, including young patients who would otherwise remain undetected. Finally, establishment of a national or regional patient registry is recommended to address the regional void in research and track outcomes over time. Adopting these strategies has great potential to improve detection of FH allowing aggressive treatment and reducing adverse cardiovascular outcomes, in both developed and developing countries.

## Conflict of Interest

The authors declare that they have no competing interests.

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