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Rheumatoid-like hand deformities and aortic valve disease in a 13-year-old girl with homozygous familial hypercholesterolemia: a case report

Anjuman Ara Rahman[1], Abhijit Datta[1], Kamal Uddin Ahmed[2], Anindita Das Barshan[3] and Mohammad Jahid Hasan[3,4*]

Abstract

Background Familial hypercholesterolemia is an autosomal dominant disorder characterized by elevated serum low-density lipoprotein cholesterol levels, tendon xanthomas, and an increased risk of atherosclerotic heart disease. Diagnosing familial hypercholesterolemia at an early age is crucial owing to its potential to lead to severe cardiovascular complications, including coronary heart disease and aortic valve disease. Early detection allows timely intervention, such as lifestyle modifications and pharmacological treatments, which can significantly reduce these risks.

Case presentation In this case report, we present a case of familial hypercholesterolemia in a 13-year-old Bangladeshi girl residing in Faridpur, Bangladesh. The patient presented with a distinctive clinical profile, including the presence of tendon xanthoma in the hands and cutaneous xanthoma in the elbow, knee, and buttocks, as well as recent development of aortic valvular diseases. In addition, she experienced joint deformity in both hands, mimicking rheumatoid arthritis, which is uncommon. The patient was diagnosed and underwent treatment through both lifestyle changes and medication. Moreover, her family received genetic counseling, and she was scheduled for regular follow-up.

Conclusion This case underscores the significance of identifying important physical signs in the diagnosis and management of familial hypercholesterolemia, particularly in settings where genetic testing may be limited. Moreover, the unique coexistence of familial hypercholesterolemia with hand joint deformity and aortic valvular heart disease serves as a clinical clue that can facilitate diagnosis and appropriate therapeutic interventions. A high index of suspicion is essential for timely diagnosis and tailored management, thus reducing the burden of atherosclerotic heart disease in affected individuals.

Keywords Familial hypercholesterolemia, Case report, Autosomal dominant disorder, Tendon xanthoma, Aortic valve disease

*Correspondence:
Mohammad Jahid Hasan
dr.jahid61@gmail.com; jahid.hasan@tdhrc.org; jahid@pirdc.org
Full list of author information is available at the end of the article

Introduction

Familial hypercholesterolemia (FH) is a hereditary dyslipidemia that is characterized primarily by elevated plasma cholesterol and low-density lipoprotein (LDL) levels, leading to an increased risk of premature cardiovascular disease. According to a meta-analysis of 11 million subjects with FH, the prevalence of FH is 0.32% (1 in 313) in the general population [1]. However, the prevalence data for FH have been recorded in only 9% of nations worldwide, suggesting a significant lack of information and underreporting of this condition [1]. Three distinct genetic abnormalities contribute to familial hypercholesterolemia (FH), including mutations in the LDL receptor gene, *APOB*, and *PCSK9*. The majority of FH cases are attributed to LDL receptor gene mutations leading to increased LDL and premature atherosclerosis [2]. The condition presents with a wide range of clinical features, such as tendon xanthomas, xanthelasma, premature coronary artery diseases, aortic valvular disease, and stroke. FH can have both homozygous (HoFH) and heterozygous (HeFH) patterns. The differentiation between homozygous and heterozygous familial hypercholesterolemia can be performed on the basis of clinical characteristics and confirmed through low-density lipoprotein cholesterol (LDL-C) levels and genetic testing. According to the American Heart Association guidelines, homozygous hypercholesterolemia (HoFH) is diagnosed when LDL-C levels exceed 400 mg/dL (10 mmol/L) and when familial hypercholesterolemia is present in one or both parents, with positive genetic testing [3]. These patients have more clinical features of premature atherosclerosis and may present early in life. In contrast, HeFH is caused by a milder increase in LDL-C levels, ranging from 160 mg/dL to 190 mg/dL, and the presence of FH or premature coronary artery disease in a first-degree relative, along with a positive genetic test [3].

Our case report illustrates a 13-year-old Bangladeshi girl who presented with rheumatoid-like hand deformities, cutaneous xanthomas, and aortic valve disease, as well as high LDL-C levels at the time of FH diagnosis.

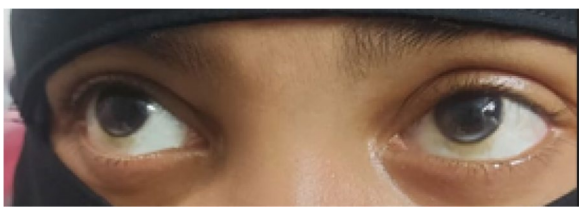

Fig. 1 Corneal arcus in both eyes (bilateral grayish-white rings in both eyes are visible along the peripheral corneal margin, sparing the limbus)

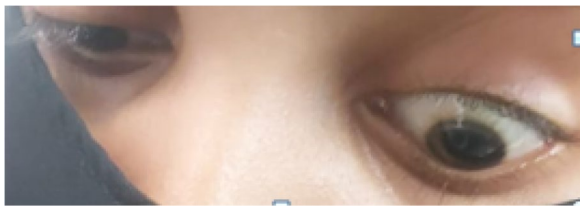

Fig. 2 Corneal arcus in left eye observed when the eye moves downward

Several studies and case reports have established that aortic valve disease is associated with FH [4, 5].

While a substantial number of case studies and recommendations are available for FHs, they are still not often recognized. Owing to limited access to investigation facilities and genetic testing centers, FH frequently remains undiagnosed in Bangladesh. A lack of comprehensive documentation of these cases in the Bangladeshi population further increases the true burden of FH. Our case report not only documents a case of familial hypercholesterolemia (FH) from Bangladesh but also emphasizes the importance of identifying physical signs and symptoms for diagnosing FH in situations where genetic testing is not possible.

Case report

We present the case of a 13-year-old Bangladeshi girl with a complex medical history of multiple tendon xanthomata in the hands and cutaneous xanthoma on the elbows, knees, and buttocks for 9 years and chest pain on exertion for 3 months. Physical examinations revealed mild anemia and a regular pulse rate of 84 beats per minute, with a blood pressure of 100/60 mmHg. The tendon xanthomata located over the dorsal aspect, proximal interphalangeal (PIP) joints of both hands caused flexion deformities of the PIP joints, while resulting in hyperextension of the distal interphalangeal (DIP) joints, closely resembling the swan neck deformities typically associated with rheumatoid arthritis, without any signs of joint inflammation. Multiple cutaneous xanthomas were observed on the extensor surfaces of the patient's elbows,

Fig. 3 Xanthelasma seen at the lateral canthus of the right eye

knees, and left buttocks (Fig 1, 2, 3, 4, 5, 6). The lesion was a well-demarcated, yellowish-brown plaque with an elevated, nodular surface and exhibited a soft, elastic texture upon palpation. The patient reported no discomfort, pain, or pruritus associated with the xanthoma.

In addition, there were corneal arcus in both eyes and xanthelasma palpebrarum around the eyelids. Examination of the fundus revealed the presence of lipemia retinalis in both eyes. Cardiovascular examination revealed a harsh systolic murmur, suggestive of aortic stenosis, confirmed by echocardiography. The patient had a history of consanguinity and familial dyslipidemia. Her father had a documented history of dyslipidemia, characterized by a serum cholesterol level of 515 mg/dL, serum triglycerides of 121 mg/dL, LDL cholesterol of 292 mg/dL, and HDL cholesterol of 47 mg/dL. In addition, her grandmother had a medical history notable for hypertension and ischemic heart disease. Her younger sibling, aged 6 years, is currently in good health. However, neither her mother nor her siblings have undergone screening for dyslipidemia.

Further laboratory investigations revealed that the patient exhibited mild microcytic hypochromic anemia, with a hemoglobin level of 10 gm/dL. Electrocardiogram (ECG) findings indicated left ventricular hypertrophy. Echocardiography revealed moderate aortic stenosis along with grade 1 aortic regurgitation. The lipid profile was repeatedly tested and LDL cholesterol level was at 950 mg/dl before treatment, with normal triglyceride levels. All secondary causes of hypercholesteremia, such as nephrotic syndrome, hypothyroidism, and drugs, were excluded.

The patient met the diagnostic criteria for familial hypercholesterolemia according to the Dutch Lipid Clinic Network (DLCN) Criteria, achieving a score of 21, where a score exceeding 8 is indicative of a definite diagnosis of familial hypercholesterolemia. The appearance of xanthomas in the first decade of life, documentation of hypercholesterolemia in the father (a lipid profile of the mother was not performed), the presence of premature atherosclerosis, and intertriginous xanthomas have all been described as markers of this homozygous type.

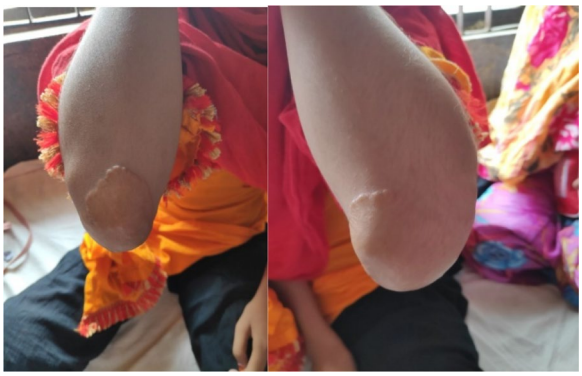

Fig. 5 Cutaneous xanthoma (multiple small, yellowish papules with an erythematous base) on the external surface of both elbows

Unfortunately, this patient was not able to undergo genetic testing for specific markers, including low-density lipoprotein receptor (LDLR), protein convertase subtilisin/kexin type 9 (PCSK9), and apolipoprotein B100 (apoB100). These genetic tests are essential for confirming the genetic mutations associated with familial hypercholesterolemia (FH). This diagnosis was made mostly on a clinical basis and included the patient's medical history, physical examination results, and lipid profile, and it followed recognized diagnostic criteria. Besides genetic testing, another limitation was that we could not measure the cholesterol level of both her mother and siblings for this diagnosis as they were not always present as her caregivers.

The patient's management was comprehensive and included dietary changes, lifestyle modifications, and pharmaceutical intervention, with 30 mg of statins and 25 mg of metoprolol. Unfortunately, other than lipid-lowering therapy, advanced treatment modalities are

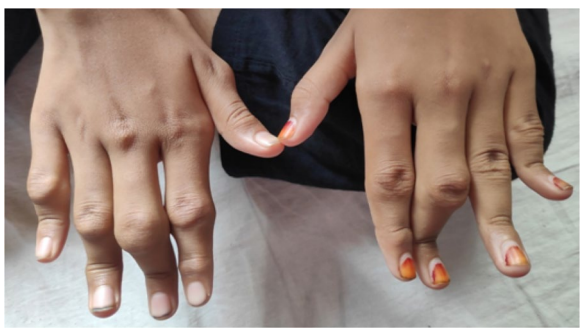

Fig. 4 Tendon xanthoma (firm, yellowish nodules located in the external surface of both hands) with deformities in both hands

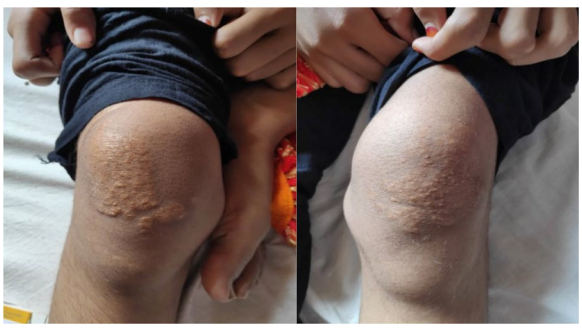

Fig. 6 Cutaneous xanthoma (multiple small, yellowish papules with an erythematous base) on both knees; cutaneous xanthoma on right knee was more prominent

not available in Bangladesh. The patient and her family received genetic counseling that emphasized the value of cascade screening, as FH has an autosomal dominant inheritance pattern. The patient will be closely monitored by a multidisciplinary team, with periodic follow-up with lipid profiling and echocardiography.

Discussion

This case report illustrates an exclusive presentation of familial hypercholesterolemia with some rare presentations, such as rheumatoid-like hand deformities, at a young age. Although genetic testing was not performed, our patient exhibited the clinical characteristics of homozygous familial hypercholesterolemia (HoFH). Early manifestations include symptoms related to cardiovascular disease, a positive family history, and the presence of widespread xanthomas. Moreover, a markedly elevated level of LDL cholesterol in the blood is a strong predictor of HoFH [6].

However, a unique clinical feature of this case was a hand deformity mimicking rheumatoid arthritis, which is not common in patients with FH. These clinical signs may lead to diagnostic dilemmas requiring the exclusion of all other differential diagnoses. This highlights the importance of clinicians being highly suspicious of familial hypercholesterolemia (FH) when they encounter such atypical symptoms, particularly in the context of family history and early-onset cardiovascular disease.

The widespread and progressive distribution of xanthomas in our patient is noteworthy and underscores the importance of strong genetic predisposition in this patient. Tendon xanthomas are infrequently encountered in routine medical practice, but are distinctive and highly indicative of familial hypercholesterolemia; they differ between those with heterozygous and homozygous FH. In individuals with homozygous FH, these xanthomas tend to develop during childhood, particularly in those aged less than 10 years, as was evident in our case [7]. In contrast, patients with heterozygous FH (HeFH) experience these conditions at a later age if left untreated [8]. In people with familial hypercholesterolemia, xanthomas are associated with a threefold greater risk of cardiovascular disease, suggesting a potential shared pathophysiology, such as that between the two disorders [9]. Cholesterol accumulation in tissues is responsible for cutaneous and tendon xanthomas, coronary artery disease, and aortic valvular diseases [10].

Our patient also developed xanthelasmata palpebrarum (XP) in a relatively early stage, which is the most commonly reported cutaneous xanthoma. According to a Japanese study, approximately 9% of patients with familial hypercholesterolemia (HeFH) are reported to have XP [11]. A large population-based cohort study in 2011 revealed an independent correlation between XP and a heightened likelihood of coronary artery disease (CAD), heart attack, and premature mortality in both the general population and patients with FH [12]. Moreover, premature corneal arcus and the onset of cardiovascular disease (CVD) at a young age are key diagnostic indicators for FH. According to the DLCN guidelines, the corneal arcus is heavily weighted, contributing four points to the diagnostic criteria [13].

Elevated levels of LDL-C, particularly at a young age, are strongly associated with the development of premature corneal arcus [14]. With respect to the relationship between the corneal arcus and CAD, the evidence is inconclusive. Data from the Framingham Heart Study suggest that corneal arcus could predict CAD or cardiovascular disease (CVD) over periods of 4 and 8 years. However, the significance of this association was of low importance once adjustments were made for age- and sex-specific risk factors [15]. Earlier studies reported that lipemia retinalis is commonly observed with hypertriglyceridemia (> 2000 mg/dl) and does not require any treatment, except for a reduction in triglyceride levels [16, 17]. However, our patient presented with lipemia retinalis with a normal triglyceride level.

Despite having cutaneous signs for several years, the patient's delayed presentation and diagnosis highlight the lack of awareness and the disparities in healthcare delivery in remote areas in Bangladesh. It also illustrates the importance of identifying physical signs for the suspicion of familial hypercholesterolemia (FH), particularly in developing countries such as Bangladesh, where genetic testing and cascade screening are often not feasible. Although genetic testing remains the definitive method for diagnosing FH, identifying these physical signs remains an invaluable approach for diagnosis. Therefore, early detection of FH and initiation of lifestyle and pharmacological treatment are imperative to prevent life-threatening complications due to premature atherosclerosis.

Conclusion

A high index of suspicion and careful clinical evaluation, including family history, detailed clinical examination, and relevant investigations are essential to determine the condition needed to institute appropriate therapy within the shortest possible time. Prompt diagnosis, meticulous treatment, strict compliance with lifestyle changes, drugs, and appropriate surgical interventions can improve the quality of life of these patients.

Abbreviations

ApoB100	Apolipoprotein B100
CAD	Coronary artery disease
CVD	Cardiovascular disease
DIP	Distal interphalangeal
DLCN	Dutch Lipid Clinic Network
ECG	Electrocardiogram
FH	Familial hypercholesterolemia
heFH	Heterozygous FH
HoFH	Homozygous familial hypercholesterolemia
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
PCSK9	Proprotein convertase subtilisin/kexin type 9
PIP	Proximal interphalangeal
XP	Xanthelasmata palpebrarum

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Author contributions
Analysis and interpretation of patient data and the literature review were performed by AAR, AD, KUA, ADB, and MJH, who guided the other authors in the reporting of this case and corrected the final manuscript. All the authors were involved in the management of the patient and read and approved the final manuscript.

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Availability of data and materials
All data are available to the lead author and can be found upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
Ethical principles were followed, and the participants provided consent before the case reports were written.

Consent for publication
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The author declares no competing interests.

Author details
[1]Bangabandhu Sheikh Mujib Medical College Hospital, Faridpur, Bangladesh. [2]Department of Cardiology, Bangabandhu Sheikh Mujib Medical College Hospital, Faridpur, Bangladesh. [3]Tropical Disease and Health Research Center, Dhaka 1100, Bangladesh. [4]Pi Research & Development Center, Dhaka 1100, Bangladesh.

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