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CASE REPORT

An Interesting Case of Familial Homozygous Hypercholesterolemia—A Brief Review

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Abstract Familial hypercholesterolemia (FH) is a form of primary hyperlipoproteinemia, is an autosomal co-dominant disorder, characterized by an increase in serum LDL cholesterol concentrations, presence of xanthomas and premature atherosclerosis. Homozygous familial hypercholesterolemia is of rare occurence in which approximately 1 in 1 million persons in the general population are affected. Here we report an interesting case of familial homozygous hypercholesterolemia for its classical presentation and rarity.

Keywords Hypercholesterolemia · Homozygous · Xanthomas

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by an elevated level of LDL-cholesterol in blood, xanthomas and premature coronary atherosclerosis [1].

Familial hypercholesterolemia is an autosomal co-dominant disorder characterized by a gene dose effect, in that the individuals with two mutant LDL receptor alleles (FH Homozygotes) are much more affected than those with one mutant allele (FH Heterozygotes). FH in Heterozygous state is more common and occurs with a prevalence of approximately 1 in 500 individuals worldwide, making it one of the most common single gene disorders, where as FH in Homozygous state is rare and occurs in approximately 1 in 1 million persons [2].

Familial hypercholesterolemia was the first genetic disorder recognized to cause Myocardial Infarction (MI). These patients are at a high risk of developing coronary heart disease and sudden death, unless the condition is recognized and treated promptly [1].

Here we report an interesting case of homozygous FH for its rarity in the prevalence rate and for academic interest and we also present a brief review of the disease.

Case Report

A 21 year old, unmarried female patient attended the dermatology OPD with complaints of multiple, small to large (2 mm to 3 cm) soft, asymptomatic yellow colored nodular lesions all over the body since the age of 2 years. Subsequently patient was referred for biochemical investigations, where an altered lipid profile was noticed, which led us to this case report.

A detailed history from the parents revealed that the patient developed the swellings since the age of 11/2 years, which gradually increased to the present size. At the age of 3 years, patient was treated by a local doctor and later took some native medicines but the symptoms did not subside. Since then she is not on any medications. The patient was born to non consanguineous parents and her developmental milestones were normal. There is no history of chest pain, breathlessness, hypertension, diabetes mellitus, hypothyroidism or any other chronic illness and she is not on any medications.

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Family history: Patient's 2 siblings and parents are healthy and do not have any skin lesions. Paternal side shows history of sudden deaths at a young age (40–45 years) (Father's elder brother and all his 3 sons have died at an early age due to possible myocardial infarction).

General examination of the patient: Height 5′1″, weight 46 kg, BMI 18.62 kg/m^2, BP 110/70 mmHg, no signs of jaundice or anemia.

Dermatological examination revealed extensive and multiple tendinous and tuberous xanthomas of varying sizes ranging from 1 to 6 cm distributed mainly over the cubital and popliteal fossae, axillae, shoulders, knees, elbows, hands and feet (Fig. 1a).

Tendinous xanthomas along the achilles tendon and extensor tendons of hands were noticed and cutaneous planar xanthomas with yellowish hue coalescing plaque like appearance along the dorsum of hands, cubital and popliteal fossae, buttocks, ankles and around the eyes were noticed (Fig. 1b). Xanthelesma palpebrarum was noted around the eye lids and her eyes showed arcus juvenalis (Fig. 1c). Dorsum of the hands showed characteristic involvement of interdigital spaces and knuckles showing the pathognomonic intertriginous xanthomas (Fig. 1d).

Laboratory investigations:

Hematological parameters: within normal limits.
Fasting blood sugar: 77 mg/dl.
PPBS: 99 mg/dl

Urea, creatinine, liver function tests and thyroid function tests were within normal limits.

Lipid profile of the patient (Table 1) shows increased total cholesterol, LDL cholesterol and LDL/HDL ratio and normal triglyceride levels.

Histopathology of the biopsy specimens confirmed the diagnosis of xanthoma.

2D-Echocardiography revealed posterior annular calcification of mitral valve, thickened and sclerosed aortic valve with mild Aortic regurgitation and mitral regurgitation.

Carotid artery intima media thickness was studied to check for atherosclerotic plaque assessment, which showed

Fig. 1 **a** Tuberous xanthoma of elbow. **b** Cutaneous xanthomas around the eye. **c** Xanthelesma palpebrarum, arcus juvenalis. **d** Intertriginous xanthomas

Table 1 Lipid profile of the patient

Total cholesterol (mg/dl)	580
Triglycerides (mg/dl)	134
LDL (mg/dl)	512
HDL (mg/dl)	93
VLDL (mg/dl)	27
LDL/HDL ratio	5.51

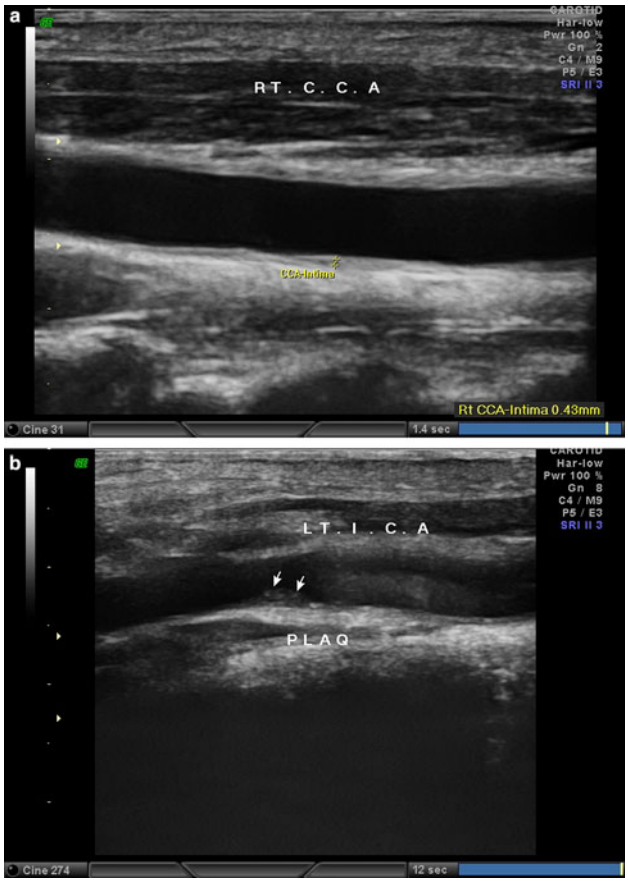

Fig. 2 **a** Increased intima media thickness. **b** Plaques in the left internal carotid artery

intimal thickening in both carotid arteries with intimal calcification and soft plaques in the left internal carotid artery, diffuse narrowing of the left vertebral artery with reduction in the flow velocity, all the features suggestive of extensive atherosclerosis (Fig. 2a, b).

Lipid profile of the other family members (Table 2), shows hypercholesterolemia in father, mother and brother, which could be a possible heterozygous FH state.

With the available laboratory data and clinical findings, it was established that the patient had Homozygous FH (type II a Frederickson's Hyperlipoproteinemia), Extensive atherosclerosis with aortic stenosis and aortic regurgitation.

She was advised low cholesterol diet, treated with Tab Atorvastatin 20 mg HS and was asked for follow up.

Discussion and Brief Review

The term xanthoma was first coined in 1869 by Smith [3]. The unique and devastating manifestations of the severe form of hypercholesterolemia was noted in the early descriptions of the condition Xanthelesma multiplex in 1879 [4]. The first familial examples of tendon or subcutaneous xanthomas associated with sudden death in young people were described by Muller and later by Harbitz, giving the name Muller–Harbitz disease for FHs [5].

On the basis of electrophoretic lipoprotein phenotype, Fredrickson et al. [6], classified primary hyperlipoproteinemia into five major types (types I–V). The monogenic inheritance of FH was first proposed in the mid-1960s by Khachadurian et al. and later Brown and Goldstein elucidated the LDL-receptor pathway, followed shortly afterwards by the cloning of the LDL-receptor gene and identification of the first mutation [7].

Familial hypercholesterolemia or Frederickson's type IIa hyperlipoproteinemia is an autosomal codominant disorder caused by >900 mutations in the LDL receptor gene present on chromosome 19, leading to the lack of functional receptors for LDL on the cell surface. This causes decreased uptake of LDL into the cells, particularly into the liver, from the blood, resulting in increased serum LDL Cholesterol. The pathophysiological problem is impaired LDL clearance and internalization, resulting in lack of inhibition of intracellular cholesterol synthesis [2].

Homozygous FH individual inherits two mutant alleles of the FH gene and consequently has six to eight folds elevation in plasma LDL cholesterol levels. It is a rare disease in which approximately 1 in 1 million persons in the general population are affected. These patients often present with the development of xanthomatosis before the first decade of life. Patients have multiple types of xanthomata, which include tuberous, sub periosteal, tendon xanthomas, elevated xanthomatous plaques and the rare but characteristic intertriginous xanthomas [8].

Xanthoma (from Greek—yellow) are plaques or nodules consisting of abnormal lipid deposition in foam cells (macrophages with phagocytosed lipid material) and collagen. Xanthomas develop because of lipid leakage from the vascular into the surrounding tissue, where macrophages subsequently phagocytose these lipids. As the cholesterol is not degraded, it accumulates within these cells, creating "foamy" macrophages. The extracellular cholesterol crystallizes into clefts and induces an inflammatory reaction with giant cells and resultant fibrosis [9].

Apart from xanthomas, familial hypercholesterolemia results in an almost 100-fold increased risk of coronary artery disease (CAD). Homozygous FH patients also develop symptomatic CAD in early childhood. Severity and prognosis of homozygous FH can be classified by

Table 2 Lipid profile of the family members

Parameters	Lipid profile of father (58 years)	Lipid profile of mother (45 years)	Lipid profile of brother (25 years)
Total cholesterol (mg/dl)	288	264	272
Triglycerides (mg/dl)	147	150	110
HDL (mg/dl)	51	61	48
LDL (mg/dl)	184	159	177

amount of LDL receptor activity in cultured fibroblast cells. Those with <2% of normal activity(receptor negative), and those with 2–25% of normal activity (receptor defective). Untreated receptor negative patients rarely survive beyond the second decade, whereas patients with defective subtype have a better prognosis but invariably develop clinically apparent atherosclerotic vascular disease by age 30 [2].

Excess plasma LDL can accumulate in arterial walls, where it becomes chemically modified and is taken up by macrophages. As the macrophages become engorged with modified LDL, they initiate the development of an atherosclerotic lesion, which, over time, can grow into an atherosclerotic plaque composed of cholesterol, cellular debris, and fibrous tissue. If the plaque ruptures, a blood clot can form and completely obstruct the artery. In a coronary artery, such an event leads to myocardial infarction [10].

Heterozygous FH is caused by the inheritance of one mutant LDL receptor allele and occur in 1 in 500 persons. Patients have 2–3 fold elevation in LDL cholesterol (200–400 mg/dl), normal triglycerides, development of mainly tendon xanthomas during III–VI decades and premature atherosclerosis leading to coronary heart disease. Untreated men with heterozygous FH have about 50% chance of having MI before age 60 [2].

Apart from LDL receptor mutations, Familial defective apolipoprotein B-100 (FDB), Autosomal Recessive Hypercholesterolemia (ARH) and sitosterolemia have phenotypic similarities with homozygous FH.

From detailed literature survey, history, investigations and detailed clinical examination the diagnosis of the rare homozygous hypercholesterolemia was done in our patient. The diagnosis of homozygous FH in our patient was based on the presence of

1. Serum cholesterol levels >500 mg/dl (>12 mmol/dl) with normal triglyceride levels.
2. Appearance of xanthomas in the first decade of life.
3. Documentation of hypercholesterolemia in both parents and in one of the siblings.
4. The presence of premature atherosclerosis, and
5. The presence of rare pathognomonic intertriginous xanthomas, which have been described as a marker of this homozygous type [11].

Due to technical constraints LDL receptor studies and genetic analysis could not be done in our patient. But an interesting and a rare observation in our patient is the presence of increased HDL levels (93 mg/dl), which is considerably higher than most other similar case histories. Available literature survey has shown low to normal HDL levels in homozygous FH cases. In FH patients the variation of HDL-C levels is thought to contribute significantly to the overall risk for CHD. However little is known about the actual contribution of genes and environment to HDL levels in FH patients. A better understanding of HDL metabolism may lead to improved cardiovascular risk assessment in these individuals [12].

A very important problem in these patients is that most of them do not feel themselves to be seriously ill until a severe myocardial infarction (often leading to sudden death) takes place during the third to fifth decades of life. Hence early diagnosis, dietary modifications and drug therapy with statins and bile acid sequestrants is very important in these patients [13].

But drug therapy has been found to be less efficacious and unresponsive in homozygous FH compared to heterozygous patients, as seen in our patient who could not tolerate the high dose statin therapy, in whom other treatment modalities like liver transplantation, LDL apheresis and portacaval shunting may have to be considered as extreme options.

This case study highlights that despite huge medical advancement FH remains seriously under-diagnosed, with a delay in the treatment. With early diagnosis and prompt treatment these patients can live longer and more productive lives. The diagnosis of FH is important not only for the prognosis of the patient but also has implications for the family members who may have inherited the same disorder. Therefore genetic counseling and screening of first-degree relatives and extended family members plays an important role in early detection and treatment.

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