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Case Report

FAMILIAL HYPERCHOLESTEROLEMIA: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Introduction: Familial Hypercholesterolemia (FH) is an autosomal co-dominant disorder characterized by elevated plasma levels of LDL-C with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. This genetic disorder results due to mutation in the LDL receptor gene located on chromosome 19.

Case report: Here we report a case of 47 year old, unmarried female patient presented with history of chest pain on & off since one month and history of swellings over dorsum of hand & elbow joints since childhood. Detailed history revealed premature deaths in the family. Her lipid profile revealed increased LDL-C (479 mg/dl), 2D-Echo shows thickened aortic valve with mitral annular calcification. Carotid doppler study showed increased intima medial thickness in both carotid arteries. CAG revealed left main disease with multivessel disease.

Treatment: She Underwent CABG and was advised life style modification, treated with antiplatelets, statins (Rosuvastatin 40 mg OD) , Ezitimibe 10 mg OD, betablockers and ACE inhibitors and advised for follow up. Her lipid profile after 6 weeks showed modest decrease in total and LDL cholesterol. She was advised LDL apheresis and liver transplantation.

Conclusion: This report is to emphasise the need to clinically recognize xanthomas and its association with elevated LDL-C, premature atherosclerosis and familial inheritance. All the family members should be screened for dyslipidemia. Early diagnosis and early treatment can prevent premature deaths due to CAD.

INTRODUCTION

Familial Hypercholesterolemia (FH) is an autosomal co-dominant disorder characterized by elevated plasma levels of low density lipoprotein cholesterol (LDL-C) with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis.[1] This genetic disorder results due to mutation in the LDL receptor gene located on chromosome 19. Individuals with two mutated LDL receptor alleles are known as Homozygous FH and one mutated allele as Heterozygous FH. Due to lack of functional LDL receptors on the cell surface, there is decreased uptake of LDL into cells mainly the liver resulting in increased serum LDL-C. Increased serum cholesterol produces several clinical manifestations, including xanthomas, xanthelasma, corneal arcus, aortic valve disease and premature coronary artery disease (CAD). These patients are managed with life style modification, lipid lowering drugs, if not responded then LDL apheresis and liver transplantation.[1] Due to the rarity of this condition, we report a case of 47 years old female who presented with chest pain, elevated LDL-C, xanthomas and severe coronary artery disease.

Case Report

A 47 year old, unmarried female patient presented with history of chest pain on & off since one month and history of swellings over dorsum of hand & elbow joints since childhood. Detailed history revealed premature deaths in the family, patient's elder brother died at the age of 32 years due to myocardial infarction (MI) and father's elder brother died at 36 years of age due to possible MI. Parents are healthy and paternal side shows history of sudden deaths at a young age.

***On general physical examination*:** BP 130/70 mmHg. No signs of anemia and jaundice. Xanthelesma palpebrarum present around the eye lids with bilateral corneal arcus.(Figure 1)

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Figure 1 Photograph of patient showing Xanthelesma palpebrarum around the eye lids and bilateral corneal arcus.

Multiple tendinous xanthomas of varying sizes were present along the achilles tendon (Figure 2), elbow joints (Figure 3), dorsum of hands (Figure 4) and cutaneous planar xanthomas with yellowish hue coalescing plaque like appearance over anterior thigh and knee joint (Figure 5).

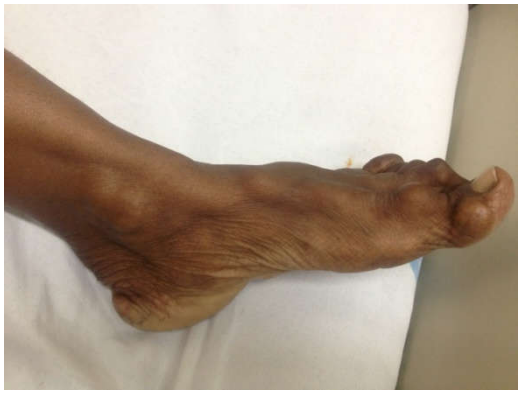


Figure 2 Photograph of patient's ankle showing xanthomas at achilis tendon.

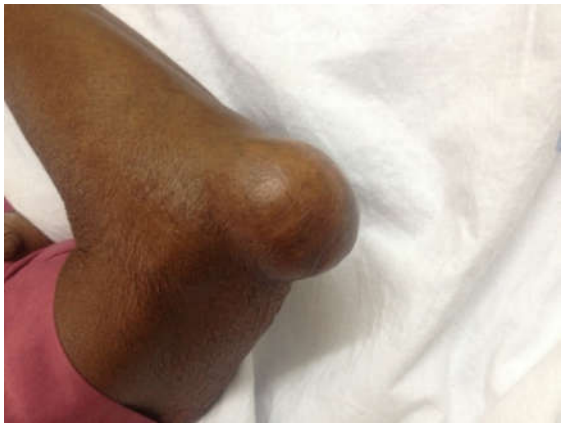


Figure 3 Photograph of patient's right elbow joint showing xanthomas.

Laboratory investigations: Her hematological parameters, renal, liver and thyroid function tests were within normal limits. Lipid profile of the patient (Table 1) shows increased total cholesterol, LDL cholesterol with normal HDL and triglyceride levels. Due to financial constraints LDL receptor studies and genetic analysis could not be done.

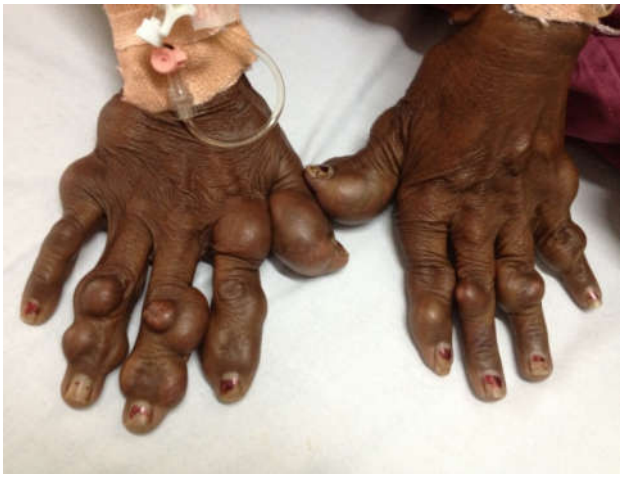


Figure 4 Photograph of patient's both hands showing multiple xanthomas.

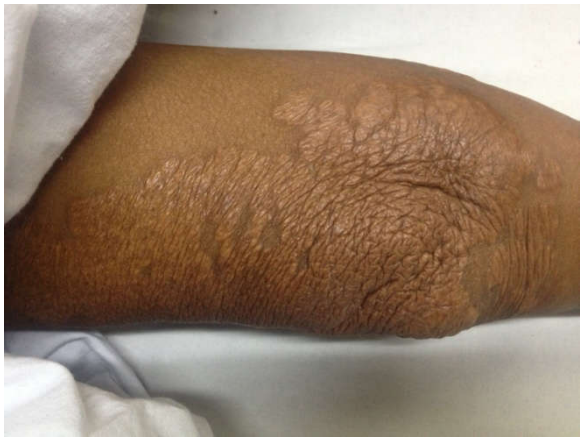


Figure 5 Photograph of patient's anterior thigh showing cutaneous planar xanthomas.

Table 1 Patient's lipid profile

1	**Total cholesterol**	**555mg/dl**
2	LDL cholesterol	479 mg/dl
3	HDL cholesterol	32 mg/dl
4	Triglycerides	190 mg/dl

Her chest X-ray, ECG and ultrasound abdomen and pelvis were normal. 2D-Echocadiography shows good biventricular function with thickened aortic valve with PPG of 16 mm Hg with mitral annular calcification and normal Pulmonary artery pressure. Her carotid doppler study showed increased intima medial thickness in both carotid arteries.(Figure 6)

Her Coronary angiography revealed left main (ostial 90% stenosis) with mutivessel disease (Proximal RCA 100%lesion, Mid LAD 80%lesion, Distal LCX 60%). (Figure 7a and 7b). Based on above findings, a familial hypercholesterolemia was considered.

***Treatment*:** She Underwent coronary artery bypass surgery (CABG) and was advised life style modification, treated with antiplatelets, statins (Rosuvastatin 40 mg OD) , Ezitimibe 10 mg OD, betablockers and ACE inhibitors and advised for follow up. Her lipid profile after 6 weeks showed modest decrease in total and LDL cholesterol.(Table 2) she was advised LDL apheresis and liver transplantation.

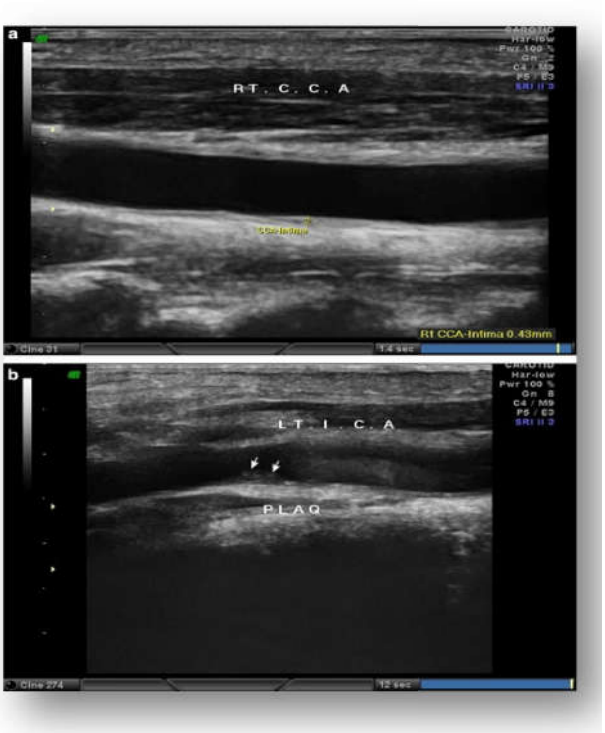
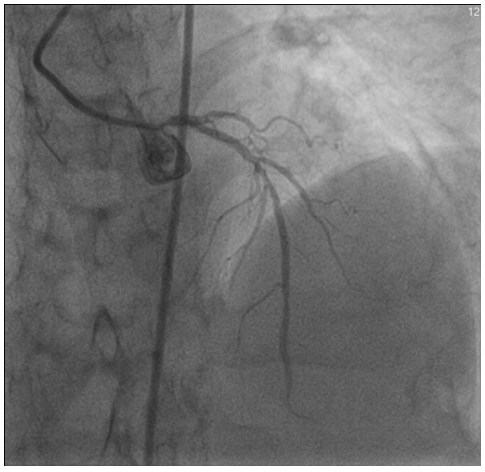


Figure 6 Carotid doppler study showed increased intima medial thickness in both carotid arteries



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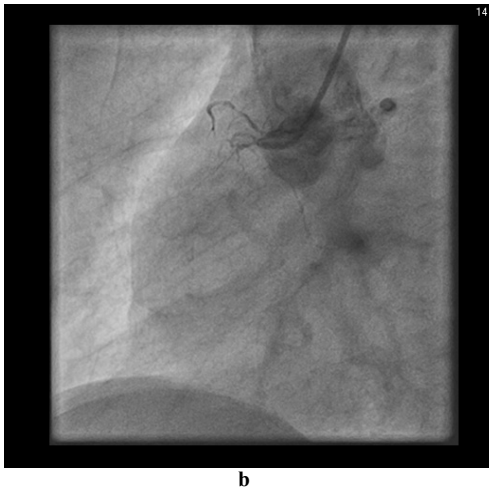

b

Figure 7(a & b) Coronary angiogram showing Left main with multivessel disease.

Table 2 Patients lipid profile after 6 weeks of statin therapy

1	**Total cholesterol**	**476mg/dl**
2	LDL cholesterol	417 mg/dl
3	HDL cholesterol	30 mg/dl
4	Triglycerides	146 mg/dl

DISCUSSION

In 1938, Dr C. Muller first described FH [2] and Myant first documented his theory that increased serum cholesterol was due to an increase in LDL particles [3] and the genetic cause for FH was described by Dr Joseph L. Goldstein and Dr Michael S. Brown. Initially, they found increased activity of HMG-CoA reductase, but studies showed that this did not explain the very abnormal cholesterol levels in people with FH. [4] The focus shifted to the binding of LDL to its receptor, and effects of impaired binding on metabolism; this proved to be the underlying mechanism for FH.[5] Subsequently numerous mutations in the protein were directly identified by sequencing.[6] They later won the 1985 Nobel Prize in Medicine for their discovery of the LDL receptor and its impact on lipoprotein metabolism. Familial hypercholesterolemia is a rare form of genetic dyslipidaemia (an autosomal codominant monogenic disease) with an incidence of about 1:500 in general population. Homozygous FH is rare, with an occurrence rate of around 1 in 100 000 individuals. The disease is caused by a mutations in the LDL-receptor gene. The genetic mutations underlying FH affect the production and processing of cell surface LDL receptors resulting in impaired hepatic clearance of circulating LDL particles, which leads to their accumulation in bloodstream.

Children with homozygous FH usually present within the first decade of life, commonly due to the presence of physical findings such as cutaneous xanthomas, xanthelasma, tendon xanthoma, corneal arcus as were observed in the present case.[7] On the contrary, the heterozygous FH subjects are usually asymptomatic with no abnormal physical findings, and are usually detected in adolescent period with elevated LDL levels prompted by a family history of premature CAD or dyslipidemia.[8]

The lipid profile is strikingly abnormal in homozygous FH subjects – the LDL cholesterol level in the range of 500 to1000 mg/dL, with reduced HDL cholesterol level between 20-40 mg/dl which conforms well with that observed in our subject. In heterozygous FH, LDL cholesterol level is above the 95th percentile for the age and gender, and is often associated with low HDL and normal triglyceride levels.[9]

Children with homozygous FH have severe and early functional and structural cardiovascular diseases including clinical CAD, aortic valve disease, and atherosclerotic aortic, carotid and peripheral vascular disease and the present case involved coronary arteries with triple vessel disease with left main disease.

Early identification of FH is best achieved by the initiation of screening between the ages of 9 and 11 years in children and no later than 20 years in adults. In families with a history of FH or premature onset CAD, screening should begin at the age 2 years.[10]

The cornerstone of therapy for high level of cholesterol is plasmapheresis, especially LDL apheresis. LDL apheresis can lower LDL-C and lipoprotein concentration safely and effectively.[11,12] LDL apheresis is done weekly once or biweekly and reported to resolve xanthomas and arrest the progression of atherosclerosis, without any major side effects in the long term.[13] Concomitant administration of high dose statins and a cholesterol absorption inhibitor results in an overall reduction of 41-72% in LDL-C. LDL apheresis can also be used in heterozygous patients who are refractory or intolerant to high dose statins.

Newer modalities of LDL-C lowering are PCSK-9 inhibitors. These are monoclonal antibodies to PCSK-9, evolocumab, alirocumab and bococizumab, are found to reduce LDL-C profoundly. Phase I and phase II studies have shown positive results, with 60-70% reduction in LDL-C levels.

CONCLUSION

Clinical identification of xanthomas and knowledge of its association with CAD is essential for every physician as early diagnosis and early treatment can prevent premature deaths due to CAD. All the family members should be screened for dyslipidemia.

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