International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

From Genes to Hearts: Exploring the Challenges and Solutions in Familial Hypercholesterolemia

Dr. Venkatesh Malali[1], Dr. Samantha Aster Pinto[2], Dr. Joel Piedade Quadros[3], Dr. L M Veeresh[4]

[1]Assistant Professor and Consultant, Department of Cardiology, MBBS, MD Medicine, DM Cardiology
Goa Medical College and Hospital, Bambolim
Email: *drvenky.malali[at]gmail.com*

[2]Junior Resident, M.B.B.S, Goa Medical College and Hospital, Department of Cardiology
Corresponding Author Email: *aster.pinto3099[at]gmail.com*
ORCID ID- 0009-0001-4106-476X

[3]Assistant Professor and Consultant, Department of Cardiology, MBBS, MD Medicine, DM Cardiology, MRCP
Goa Medical College and Hospital, Bambolim
Email: *joelquadros11[at]gmail.com*

[4]M.B.B.S. M.D Medicine, DM Cardiology, Goa Medical College and Hospital, Department of Cardiology
Email: *veeresh953863[at]gmail.com*

Running Title: *Challenges and Solutions in Familial Hypercholesterolemia*

Abstract: ***Type IIa familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels, xanthomas, and an increased risk of premature cardiovascular disease [1,2]. This case describes a 13-year-old girl presenting with tuberous xanthomas associated with cardiovascular abnormalities. The case was ultimately diagnosed as Type IIa FH, emphasizing the importance of recognizing familial hypercholesterolemia with histopathological and genetic analysis in patients with characteristic cutaneous and cardiovascular findings to initiate timely intervention and prevent cardiovascular sequelae.***

Keywords: Familial hypercholesterolemia, tuberous xanthomas, xanthogranulomas, cardiovascular abnormalities

1. Introduction

Familial hypercholesterolemia is caused by mutations in the low-density lipoprotein receptor gene (LDLR) [2,3]. Homozygous familial hypercholesterolemia (HoFH) is a rare genetic condition, with an estimated incidence of 1 in 1,000,000 individuals globally, whereas heterozygous familial hypercholesterolemia (HeFH) affects approximately 1 in 500 individuals [2]. The phenotype of FH can also be seen with mutations in the genes that code for proprotein convertase subtilisin kexin 9 (PCSK9) and apolipoprotein B (APOB) [3,4]. Individuals with phenotypic FH who do not have mutations in one of these key genes may have polygenic defects [1,3]. FH is inherited with a gene-dosing effect, in which homozygotes are more severely affected than heterozygotes [2]. Homozygotes often present in childhood with xanthomas, premature coronary artery disease, and survival of less than 20 years of age if untreated [2,5].

Type IIa FH is characterized by elevated LDL-C levels, xanthomas, aortic valve involvement, and an increased risk of premature cardiovascular disease [2,5]. The clinical presentation of Type IIa FH can vary widely, posing a diagnostic challenge [3,5].

Here, we present a case report of Type IIa FH with distinct clinical features, emphasizing the importance of comprehensive evaluation and genetic analysis in reaching an accurate diagnosis.

2. Case Report

A 13-year-old girl, born to parents who are third-degree relatives, presented at the pediatric outpatient department with concerns about insufficient height and weight gain since the age of 5. She also experienced easy fatiguability and breathlessness during outdoor activities. The patient noticed a significant delay in her growth compared to her two younger brothers, surpassing her height by the age of 7. Additionally, she observed the development of yellowish papular and nodular lesions starting around her ankles and spreading to her forearms, trunk, finger web spaces, and upper back. The largest lesion measured 8×5 cm. It was not associated with redness, itching, or pain. No similar occurrences have been reported in any other family member.

Examination findings revealed hyperpigmented, yellowish to orange plaques. These hyperpigmented papules were noted over the extensor surface of the neck, scapular area, arms, webbed spaces of the fingers, behind the knee joint, and feet. No lesions were noted on the face, chest, and abdomen (Figures 1–6).

Routine investigations, including a complete hemogram, X-ray, and fundus examination, were unremarkable. The lipid profile showed elevated levels, with total cholesterol at 716 mg/dL and LDL at 675 mg/dL. Triglycerides and other lipoprotein fractions were within normal limits. Serum homocysteine and cortisol levels were normal. An echocardiogram revealed a trileaflet thickened aortic valve (Vmax=2.18 m/s) with moderate aortic regurgitation and

intermediate flow reversal in the descending aorta, along with a mildly dilated left atrium (Figure 8).

Histopathological examination indicated tuberous xanthomas, characterized by nodular granulomatous infiltrates in the upper and deep dermis, consisting of pale-stained histiocytes with abundant foamy cytoplasm, some forming giant cells. Exome sequencing revealed a homozygous mutation in exon 9 of the LDLR gene, explaining the observed phenotype (Figure 7). Treatment with lipid-lowering agents rosuvastatin and ezetimibe was initiated. CT aortogram showed circumferential wall thickening with specs of intimal calcification in ascending aorta and short segment narrowing in right carotid bulb causing < 50% stenosis suggestive of atherosclerotic cardiovascular disease (ASCVD) (Figure 9)

After one year of treatment, the patient remains dyslipidemic, but there have been no reports of new lesions or an increase in the size of existing lesions. Her total cholesterol levels revealed a persistently elevated level of 629 mg/dL. LDL apheresis was considered as a treatment option; however, it was not feasible. Her siblings were also advised to get evaluated for the disease.

3. Conclusion

Familial hypercholesterolemia (FH) is a genetic condition characterized by elevated LDL cholesterol levels from birth, tendon xanthomas in untreated adults and children with homozygous FH, and an increased risk of premature ASCVD [1,2]. Early identification and proper treatment of FH are crucial for reducing mortality and delaying the onset of coronary heart disease in affected individuals [2,5].

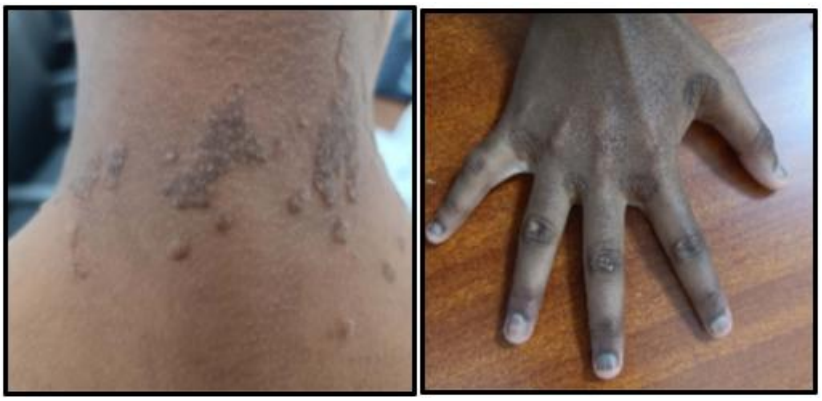
A retrospective cohort study using the Catalan primary care system showed that, in primary prevention, patients with FH had higher incidences of atherosclerotic cardiovascular disease (ASCVD) and coronary heart disease (CHD) than the normolipidemic group. Specifically, FH patients had 14.9/1000 and 5.8/1000 person-years for ASCVD and CHD, respectively, compared to 7.1/1000 and 2.1/1000 person-years in the normolipidemic group [5].

Despite treatment with statins, FH patients still face significantly higher cardiovascular risks compared to the general population, with the greatest excess risk observed in younger individuals [5]. Diagnosis of the above patient was made with the help of histopathological findings and genetic study. The histopathological study revealed tuberous xanthomas. These findings were confirmed with subsequent genetic testing elucidating underlying Type IIa homozygous FH [2,3]. Recognition of underlying FH is crucial due to its implications for cardiovascular health and necessitates aggressive lipid-lowering therapy [6].

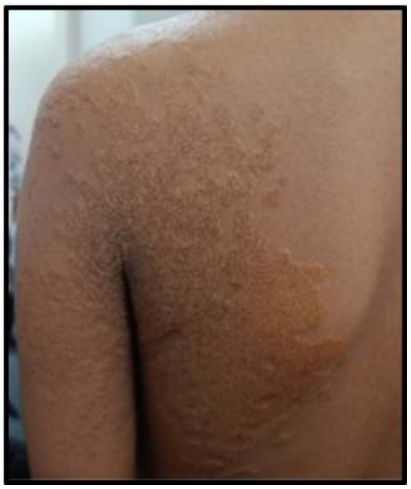
Despite the patient being on statin and ezetimibe therapy, there was marginal improvement in LDL values. Additional treatments like PCSK9 inhibitors and LDL apheresis need to be explored more as treatment options for further management and optimal treatment [6].

References

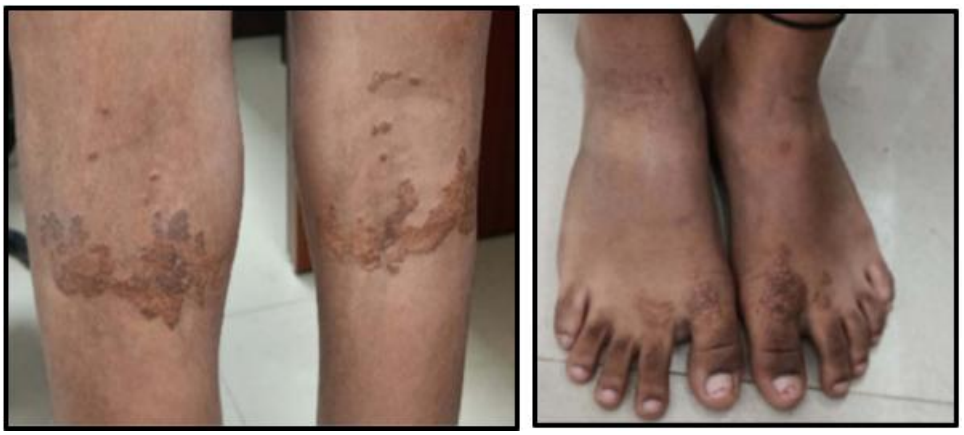
[1] **Nordestgaard BG, Chapman MJ, Humphries SE, et al.** Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J*. 2013;34(45):3478–3490a. (Covers inheritance, underdiagnosis, polygenic FH.)
[2] **Cuchel M, Bruckert E, Ginsberg HN, et al.** Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. *Eur Heart J*. 2014;35(32):2146–2157. (Incidence, clinical features, prognosis, management strategies.)
[3] **Soutar AK, Naoumova RP.** Mechanisms of disease: genetic causes of familial hypercholesterolemia. *Nat Clin Pract Cardiovasc Med*. 2007;4(4):214–225. (Genetics of LDLR, APOB, PCSK9, phenotype variability.)
[4] **Abifadel M, Varret M, Rabès JP, et al.** Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34(2):154–156. (Seminal discovery of PCSK9 mutations in FH.)
[5] **Ference BA, Ginsberg HN, Graham I, et al.** Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. *Eur Heart J*. 2017;38(32):2459–2472. (Strong, modern evidence linking LDL to ASCVD risk in FH.)
[6] **Mach F, Baigent C, Catapano AL, et al.** 2019 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J*. 2020;41(1):111–188. (Current gold standard for FH treatment and LDL-lowering strategies.)



Figures 1 & 2: Papules at the nape of the neck and finger web spaces



Figures 3: Nodules on shoulder and scapula



Figures 4 & 5: Papules and nodules in the popliteal area and bilateral feet

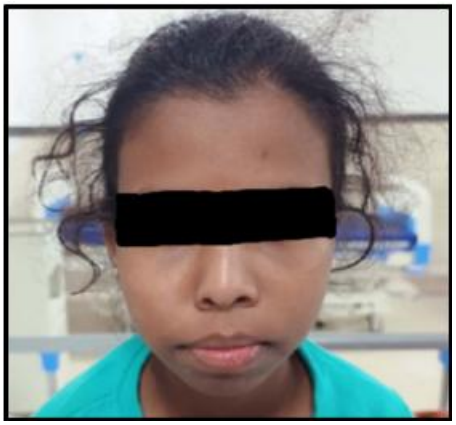


Figure 6: Absence of nodules on the face

Gene (Transcript)	Location	Variation	Zygosity	Classification'	Disease (OMIM)	Inheritance
LDLR (NM_000527.5)	Exon 9	c.1285G>A (p.Val429Met)	Homozygous	Pathogenic	Hypercholesterolemia, familial, 1 (143890); LDL cholesterol level QTL2 (143890)	Autosomal dominant. Autosomal recessive

Figure 7: Exome sequencing result

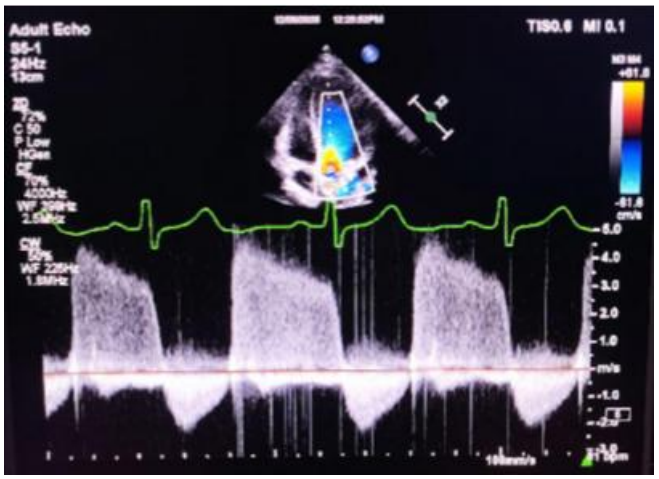


Figure 8: Continuous wave doppler across aortic valve showing aortic regurgitation with raised Vmax.

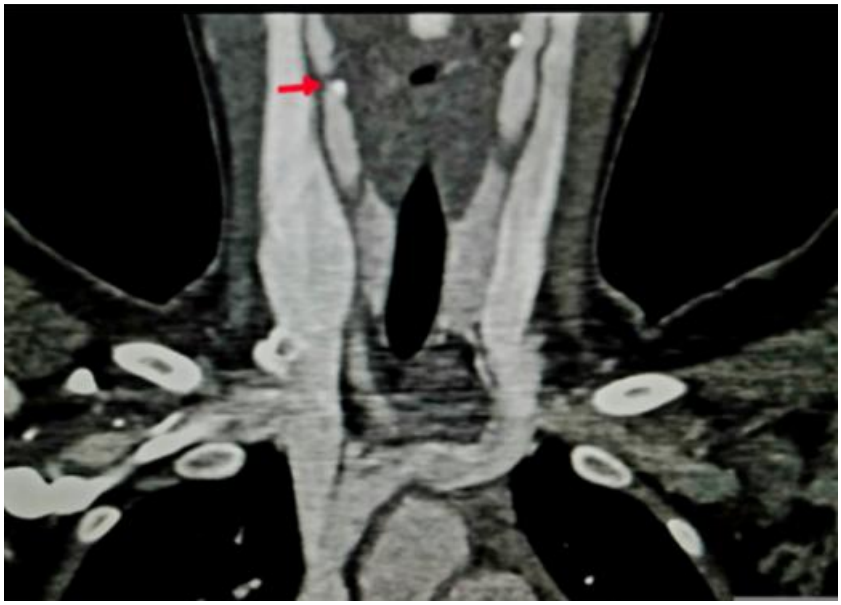


Figure 9: Short segment narrowing noted at the right carotid bulb extending for a length of 7mm causing <50% stenosis