Journal of Cardiology Research and Endovascular Therapy

PRIME OPEN ACCESS

Volume 1, Issue 1

Research Article

Date of Submission: 05 February, 2025
Date of Acceptance: 28 March, 2025
Date of Publication: 03 April, 2025

Premature Coronary Artery Disease Due to Familial Hypercholesterolemia in a 26 Year Female

Kanika Kukreja*

India

Corresponding Author:
Kanika Kukreja, India.

Citation: Kukreja, K. (2025). Premature Coronary Artery Disease Due to Familial Hypercholesterolemia in a 26 Year Female. *J Cardiol Res Endovasc Ther, 1*(1), 01-05.

Abstract
26 years old Female, no addiction and no known comorbidities, presented with complaints of chest pain for last 2 months, retrosternal, insidious in onset, gradually progressing and radiating to back and both the arms, mostly on exertion like hurrying on a level or walking upstairs. Upon examination patient had xanthelasmas over both upper eyelids and elbow and corneal arcus. Lipid profile testing showed very high LDL levels. CT angiography done showed LM disease with triple vessel disease. patient was advised CABG and lipid lowering therapy. Familial hypercholesterolemia, an autosomal dominant genetic disorder carries the risk of premature coronary artery disease in the affected people and early identification of FH is necessary.

Keywords: Case Report, Premature Coronary Artery Disease, Familial Hypercholesterolemia and Coronary Artery Disease

Introduction
Familial hypercholesterolemia (FH) is a common yet underdiagnosed autosomal dominant disorder which is characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C) and if untreated leads to early-onset atherosclerosis and increased risk of cardiovascular events [1]. Affected men and women who are untreated have a 30% to 50% risk of a fatal or nonfatal cardiac event by ages 50 and 60 years, respectively. The defect lies in the LDL receptors located in the liver and other organs owing to a possible mutation occurring in the LDL receptor gene located in the short arm of chromosome 19. However, the disease remains seriously underdiagnosed. Early detection and aggressive treatment are the keys. Screening of first-degree relatives play an important role and needs to be emphasise.

Patient Information
Our patient presented at the age of 26 year with the complaints of exertional chest pain on exertion for past two months. Even though she had cutaneous xanthomas from past 10 years and her brother too had coronary artery disease and xanthelasmas, her condition remained underdiagnosed emphasising the need of early diagnosis and treatment of patients with familial hypercholesterolemia.

Case Presentation
26 years old Female, from a non-consanguineous marriage, no addiction and no known comorbidities presented with complaints of chest pain for last 2 months, retrosternal, insidious in onset, gradually progressing and radiating to back and both the arms, mostly on exertion like hurrying on a level or walking upstairs initially NYHA II and progressed to NYHA III. there were no complaints of orthopnoea, PND, palpitation, dizziness or syncope. there was no history of cough and expectoration, swelling of bilateral lower limbs. She had xanthelasmas for the past 10 years but never sought any treatment for the same. Her elder brother was also diagnosed with CAD at the age 44 year with high cholesterol levels and presence of xanthelasmas.

Clinical Findings
On examination patient was Clinically stable with a pulse rate of 76/min, normal blood pressure and absence of pallor, pedal oedema, clubbing or cyanosis. she was average built with presence of xanthelasmas over bilateral upper eyelids

and right cubital fossa. Corneal arcus was present. There were no tendon xanthomas. Cardiovascular and other systemic examination were normal.

Figure 1: Clinical Examination

A: Patient had xanthelasma present on B/L upper eyelids.
B: Patient also had xanthelasmas on right cubital fossa.
C: Patient's brother showing xanthelasma.

Diagnostic Assessment

The lipid profile depicted a total cholesterol level of 697 mg/dl, triglycerides of 183 mg/dl, HDL of 45 mg/dl, LDL of 496 mg/dl. Her CBC and other biochemical investigations were within normal limits. ECG showed normal sinus rhythm and no specific changes. 2D ECHO done showed normal biventricular function. Dutch Lipid Clinic Network Score of this patient was 14 giving a definite diagnosis of familial hypercholesterolemia

Coronary Angiography (Figure 2) was done which showed LMCA Plaquing 30-40%, LAD showed Ostial plaquing 30-40%, proximal 80-90 % stenosis, bifurcation lesion with D1(MEDINA 1,1,1), mid LAD diffuse disease maximum 90-95% stenosis. D1 showing Ostio-proximal 90% stenosis. LCX was non-dominant having Proximal 40-50 % plaquing, distal LCX plaquing and OM1(major OM) with Proximal 90-95% stenosis. RCA: Ostial plaquing 50%, proximal diffuse disease, maximum 80-90%, mid RCA 100% occlusion, retrogradely filling from Left Injection. She was advised CABG and started on lipid lowering therapy.

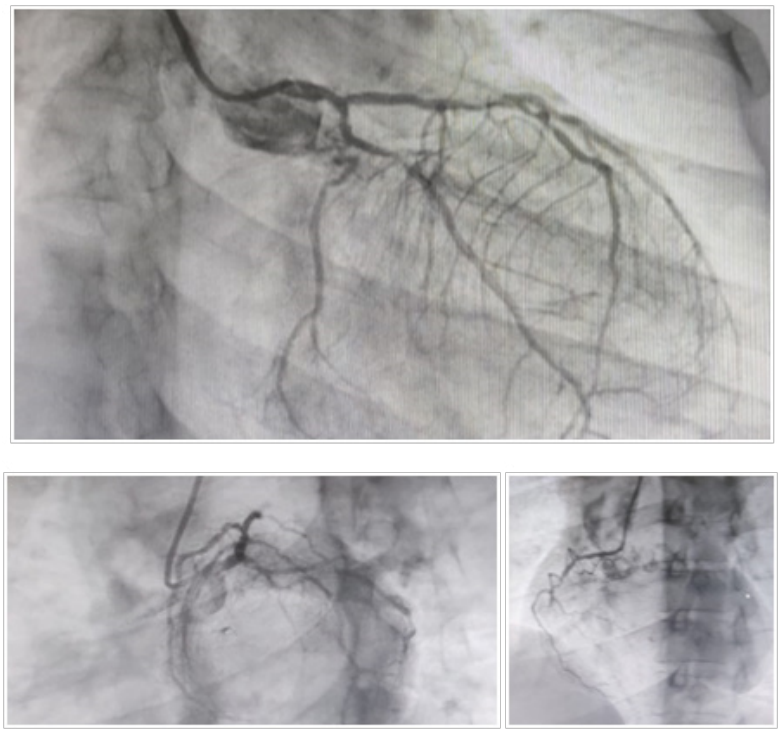

Figure 2: Coronary Angiography of the Patient

A: RAO caudal view showing showed Ostial plaquing 30-40%, proximal 80-90 % stenosis, bifurcation lesion with D1(MEDINA 1,1,1), mid LAD diffuse disease maximum 90-95% stenosis. D1 showing Ostio-proximal 90% stenosis. LCX: Non-Dominant having Proximal 40-50 % plaquing, distal LCX plaquing and OM1(major OM) with Proximal 90-95% stenosis.
B: LAO Caudal view showing LMCA Plaquing 30-40%.
C: LAO 30 view showing Ostial plaquing 50%, proximal diffuse disease, maximum 80-90%, mid RCA 100% occlusion, retrogradely filling from Left Injection.

Therapeutic Intervention

Patient was advised CABG as first line treatment for LM + TVD. Lifestyle modification was advised including dietary modification, physical activity and weight reduction. Optimised medical therapy and lipid lowering therapies were started. Antilipidemic Treatment was initiated with high-intensity statin therapy in combination with ezetimibe (Tablet rosuvastatin 40 mg and Tablet ezetimibe 10 mg) with a goal of >50% reduction of LDL-C from baseline and an LDL-C <50 mg/dl.

Follow Up and Outcomes

Her symptoms improved with improvement of functional class III to II. optimised medical therapy including dual antiplatelets and antianginal but LDL levels remain in same range after follow up period of 2 month. She was advised further intensification of oral antilipidemic drugs (Bempedoic acid) with further follow up and plan for PCSK9 inhibitor and LDL apheresis.

Discussion

Familial hypercholesterolemia is a group of inherited genetic defects that lead to the severe elevation of serum cholesterol concentrations. Clinically familial hypercholesterolemia is diagnosed by a high serum level of low-density lipoprotein (LDL) cholesterol and genetically is characterized into two subgroups: (1) autosomal dominant (AD), (2) codominant transmission with 90% or higher penetrance1 but it also has an autosomal recessive AR mode of inheritance. The established AD genes are: low-density lipoprotein receptor (LDLR), apolipoprotein B-100 (APOB) or proprotein convertase subtilisin/kexin type 9 (PCSK9). Mutations in one allele of either of these genes may lead to the heterozygous FH (HeFH) phenotype and mutations in both alleles may lead to the more severe homozygous FH (HoFH) phenotype.

The LDL receptor adaptor protein 1 (LDLRAP1) gene is responsible for the AR form of FH. It is an underdiagnosed genetic inherited condition that may lead to premature coronary artery disease (CAD) [2]. However, recent studies suggest the prevalence is vastly underestimated [3]. In FH, the mutation of the LDL receptor prevents efficient uptake of LDL by peripheral tissue leading to slow clearance of LDL from the circulation, which delay in heterozygotes could be 2.5 to 4.5 times and 6 to 8-fold in homozygotes. Till date, more than 400 different mutations resulting in the FH phenotype have been described [4]. Plasma levels of LDL-C are elevated at birth and remain so throughout life. Plasma TG levels are typically normal, and HDL-C levels are normal or reduced FH is associated with a much higher risk for the development of CAD than are other forms of hypercholesterolaemia [4].

Almost five percent of all patients who suffer from CAD are FH – heterozygotes. FH is clinically diagnosed on the basis of a weighted combination of physical findings, personal or family history of hypercholesterolemia, early-onset ASCVD, and the concentration of circulating LDL-C. Extensor tendon xanthomas (typically Achilles, sub patellar, and hand extensor tendons) with extremely elevated LDL-C levels are considered specific for FH. Homozygotes are found approximately 1 in a million. The total cholesterol values are much higher in the homozygous variant (500–1000 mg/dl) as compared with those of heterozygous forms (325–450 mg/dl) [5].

Incidence of premature CHD is much earlier in the homozygous forms (second decade) and xanthomas occur in the first decade. Various scores are available for diagnosis of familial hypercholesterolemia and Dutch Lipid Clinic Network Score (DLCNS; Table 1) is one of them and is used to make a probable or definite clinical diagnosis of FH on the basis of phenotypic criteria [6]. It is based on several key factors including the patient's family history of premature cardiovascular disease (CVD), their personal CVD history, their untreated LDL-C levels and physical stigmata such as tendon xanthomas or arcus cornealis. According to the National Institute for Health and Clinical Excellence (NICE) guidelines, persons who have a family history of early coronary heart disease and high LDL-C should be suspected of having FH. According to these guidelines, a diagnosis of FH in young people is not ruled out if they do not exhibit physical symptoms like tendinous xanthoma and arcus cornealis [7].

Dutch Lipid Network Criteria for Diagnosis of FH	
Criteria	**Score**
Family history	
Premature CVD (men <55 y old, women <60 y old) in first-degree relative, OR	1
LDL >95th percentile in first-degree relative AND/OR	1
Tendon xanthoma and/or arcus cornealis in first-degree relative, OR	2

LDL >95th percentile in children <18 y old	2
Personal history	
Premature CAD in patient (men <55 y old, women <60 y old)	2
Premature cerebral or peripheral vascular disease (men <55 y old, women <60 y old)	1
Clinical Examination	
Tendon Xanthomas	6
Arcus Cornealis at age <45	1
LDL cholesterol	
>330 mg/dL (8.5 mmol/L)	8
250–329 mg/dL (6.5–8.5 mmol/L)	5
190–249 mg/dL (4.9–6.4 mmol/L)	3
155–189 mg/dL (4.0–4.9 mmol/L)	1
Presence of functional LDL-R mutation (in the LDL-R, ApoB, or PCSK9 gene)	8

Table 1: Dutch Lipid Network Criteria for Diagnosis of FH

Early initiation of lifestyle interventions and lipid lowering therapy are critical for management of familial hypercholesterolemia. For Homozygous familial hypercholesterolemia treatment should be started in the first year of life or at an initial diagnosis, often with ezetimibe and other lipid-modifying therapy. As it is difficult to achieve LDL-C targets, adjunctive lipoprotein apheresis is recommended where available, preferably started by age 5 and no later than 8 years. Patients should start on a high-intensity statin and ezetimibe rather than statin monotherapy, but most will require additional therapies to attain goal [8]. Within 8 weeks proprotein convertase subtilisin/kexin type 9 (PCSK9)-directed therapy should be considered where available. Response to these treatments is dependent on the degree of residual LDL receptor activity. PCSK9 monoclonal antibody therapy (evolocumab or alirocumab) is effective in many patients with HoFH. If patients show >15% additional LDL-C reduction, PCSK9-directed therapy may be continued, but if response is poor, can be stopped [9].

The advent of recently approved medications, such as Inclisiran and Bempedoic acid, either as monotherapy or as add-on therapy to statins, has further enhanced the therapeutic armamentarium that can be used in FH patients [10]. Bempedoic acid inhibits adenosine triphosphate-citrate lyase, i.e., it acts at an earlier level in the cascade of cholesterol biosynthesis compared to statins. Novel therapies including Lomitapide, an oral inhibitor of the microsomal triglyceride transfer protein affecting the production of very low-density lipoproteins, can be added with reduction plasma LDL-C levels by 60% can be achieved, Lp(a) by 15% at 26 weeks [11]. Other novel therapy ANGPTL3 monoclonal antibody Evinacumab can be used HoFH aged at least 12 years (15 mg/kg intravenously every 4 weeks) which reduces LDL-C by ~50% on top of maximally tolerated lipid-lowering therapy with or without Lipoprotein Apheresis [12]. Lipoprotein apheresis (LA) is foundational in children and adults with HoFH, adjunctive to other lipid-lowering therapy. LA is usually performed fortnightly or even weekly. If not available, plasma exchange may be considered [13].

The index case had a TC of 183 mg/dl with an LDL-C of 496 mg/dl. There was positive family history of coronary artery disease, xanthelasmas with arcus cornealis with abnormal lipid profiles. This patient was suffering from angina for the past 3 months. Her angiography revealed triple vessel disease and Dutch Lipid Clinic Network Score of this patient was 14 giving a definite diagnosis of familial hypercholesterolemia. We report this case to emphasize that FH patients are at increased risk of premature ASCVD; therefore, timely detection and early treatment initiation is of major importance. Early disease diagnosis and family screening may aid in both preventing the disease's progression and detecting it early.

Reference

1. Vaezi Z, Amini A. Familial Hypercholesterolemia. [Updated 2022 Sep 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
2. Sharma, S. K., Makkar, J. S., Bana, A., Sharma, K., Kasliwal, A., Sidana, S. K., ... & Gupta, R. (2022). Premature coronary artery disease, risk factors, clinical presentation, angiography and interventions: Hospital based registry. *Indian heart journal, 74*(5), 391-397.
3. Nordestgaard, B. G., Chapman, M. J., Humphries, S. E., Ginsberg, H. N., Masana, L., Descamps, O. S., ... & European Atherosclerosis Society Consensus Panel. (2013). Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *European heart journal, 34*(45), 3478-3490.
4. Brown MS, Herz J, Goldstein JL. LDL-receptor structure. Calcium cages, acid baths and recycling receptors: LDL-receptor structure. *Nature* [Internet]. 1997;388(6643):629–30.
5. Chung, M. H., Chen, K. W., Chen, J. F., Lu, W. T., Sun, J. H., & Lin, J. D. (1999). Identification of familial hypercholesterolemia in Taiwan: report of eleven cases. Changgeng yi xue za zhi, 22(3), 460-467.
6. Lee SH. Update on familial hypercholesterolemia: Diagnosis, cardiovascular risk, and novel therapeutics. *Endocrinol Metab (Seoul) [Internet]. 2017;32*(1):36–40.

7. Pilling, S., Gray, J., Josh, J., Marsden, G., Treadwell, J., Ali, P., ... & Taylor, L. (2017). Familial hypercholesterolaemia: identification and management. *Evidence reviews for case-finding, diagnosis and statin monotherapy.*
8. Cuchel M, Raal FJ, Hegele RA, Al-Rasadi K, Arca M, Averna M, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J [Internet]. 2023;44*(25):2277–91.
9. Santos RD, Stein EA, Hovingh GK, Blom DJ, Soran H, Watts GF, et al. Long-term evolocumab in patients with familial hypercholesterolemia. *J Am Coll Cardiol [Internet]. 2020;75*(6):565–74.
10. Anagnostis P, Antza C, Florentin M, Kotsis V. Familial hypercholesterolemia and its manifestations: Practical considerations for general practitioners. Kardiol Pol [Internet]. 2023;81(11):1081–8.
11. Hussain, M. M., Rava, P., Walsh, M., Rana, M., & Iqbal, J. (2012). Multiple functions of microsomal triglyceride transfer protein. *Nutrition & metabolism, 9*, 1-16.
12. Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, et al. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med* 2020;383: 711–720.
13. Stefanutti, C., Julius, U., Watts, G. F., Harada-Shiba, M., Cossu, M., Schettler, V. J., ... & Williams, H. (2017). Toward an international consensus—Integrating lipoprotein apheresis and new lipid-lowering drugs. *Journal of clinical lipidology, 11*(4), 858-871.