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RESEARCH ARTICLE

PREMATURE CORONARY ARTERY DISEASE DUE TO FAMILIAL HYPERCHOLESTROLEMIA IN A 26 YEAR FEMALE

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Abstract

Background:Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder characterized by lifelong elevation of low-density lipoprotein cholesterol(LDL C),leading to premature atherosclerotic cardiovascular disease.Despite being relatively common,FH remains underdiagnosed and undertreated, often presenting with advanced coronary artery disease (CAD) at a young age.

Case Presentation: We report a 26-year-old woman presenting with exertional chest pain for two months.She had long standing xanthelasmas and a positive family history of premature CAD in her elder brother. On examination, xanthelasmas and corneal arcus were noted. Her lipid profile revealed total cholesterol of 697 mg/dL and LDL-C of 496 mg/dL. The Dutch Lipid Clinic Network Score was 14, confirming definite FH. Coronary angiography showed severe triple vessel disease with critical stenoses involving the left anterior descending artery, obtuse marginal branch, and right coronary artery. She was initiated on high-intensity statin therapy (rosuvastatin 40 mg) with ezetimibe and advised coronary artery bypass grafting (CABG). Despite symptomatic improvement, LDL-C levels remained markedly elevated on follow-up, necessitating consideration of bempedoic acid, PCSK9 inhibitors, and LDL apheresis.

Conclusion: This case illustrates the aggressive natural history of FH, manifesting as premature CAD in a young female patient. It underscores the need for heightened clinical suspicion, early diagnosis, and initiation of intensive lipid-lowering therapy to prevent adverse cardiovascular outcomes.Family screening and newer therapeutic options, including PCSK9 inhibitors and LDL apheresis, play a pivotal role in optimizing management.

Introduction:-

Familial hypercholesterolemia (FH) is a common but underdiagnosed autosomal dominant disorder marked by lifelong elevated LDL-C levels, leading to early atherosclerosis and increased cardiovascular risk.[1] If untreated, up to 50% of affected individuals may experience major cardiac events by midlife. The condition is usually caused by mutations in the LDL receptor gene on chromosome 19. Early diagnosis, aggressive lipid-lowering treatment, and screening of first-degree relatives are critical to improving outcomes.

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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 arterydisease 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:
The patient appeared clinically stable, with a heart rate of 76 bpm and normal blood pressure. No peripheral signs such as pallor, cyanosis, clubbing, or pedal edema were noted. 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.

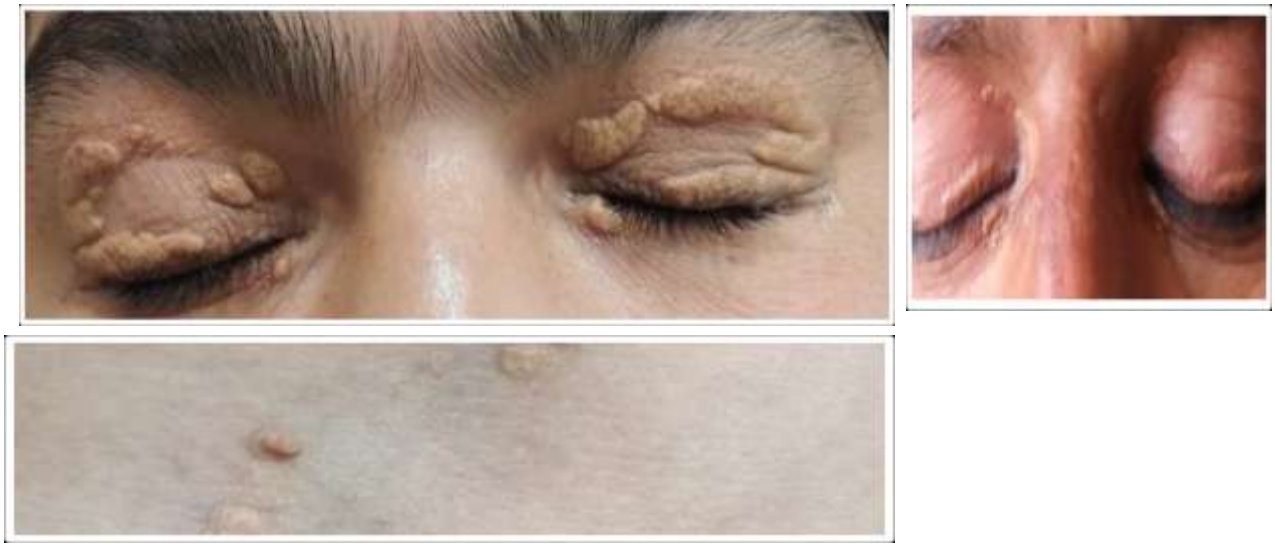

Figure 1: Clinical examination A: Patient had xanthelasma present on B/L upper eyelids B Patient also had xanthelasmas on right cubital fossa. C: Patient's brother showing xanthelasma

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 hypercholesterolemiaCoronary Angiography(Figure 2) was done which showed LMCA plaquing 40-50%, 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.

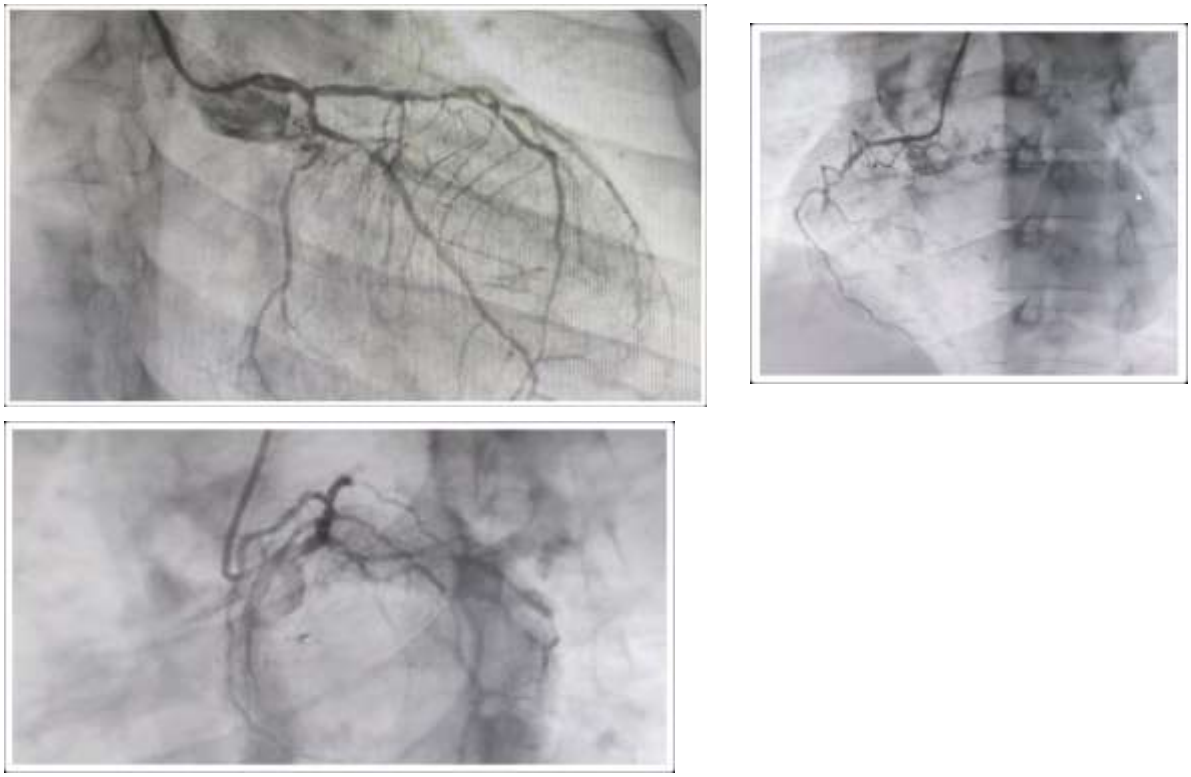

FIGURE 2: Coronary Angiography of the patient A: RAO caudal view showing showed Ostial plaquing 30-40%, proximal 80-90 % stenosis, bifurcation lesion with D1(MEDINA 1,1,1), mid LAD diffuse disease maximum 90-95% stenosis. D1 showing Ostio-proximal 90% stenosis. LCX : Non-Dominant having Proximal 40-50 % plaquing, distal LCX plaquing and OM1(major OM) with Proximal 90-95% stenosis. B:LAO Caudal view showing LMCA Plaquing 30-40%. C: LAO 30view 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 improvedwith 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 furtherintensification of oral antilipidemic drugs (Bempedoic acid) with further follow up and plan for PCSK9 inhibitor and LDL apheresis.

Discussion:-

Familial hypercholesterolemia (FH) is a genetic disorder characterized by markedly elevated LDL cholesterol levels from birth, increasing the risk of premature coronary artery disease (CAD). It is typically inherited in an autosomal dominant (AD) manner, though an autosomal recessive (AR) form also exists. Mutations in the LDLR, APOB, or PCSK9 genes cause the AD type, while LDLRAP1 mutations lead to the AR variant. A single mutated allele results in heterozygous FH (HeFH), while mutations in both alleles cause the more severe homozygous FH (HoFH). Due to defective LDL receptors, LDL clearance from the bloodstream is significantly impaired—delayed 2.5 to 4.5 times in HeFH and 6 to 8 times in HoFH. Despite being a major cardiovascular risk factor, FH remains underdiagnosed, and recent research suggests its prevalence is higher than previously believed. Over 400 genetic mutations have been linked to FH. [2,3] LDL-C levels are high from birth, while triglycerides are usually normal and HDL-C may be low. FH confers a higher risk of CAD than other lipid disorders, with HeFH accounting for nearly 5% of CAD

cases.[4] Diagnosis is based on LDL-C levels, family history, and physical signs such as tendon xanthomas (notably on the Achilles, hands, and knees). Homozygous FH is rare (1 in 1 million) and presents with total cholesterol levels of 500–1000 mg/dL, while heterozygous forms range from 325–450 mg/dL. [5] Homozygous familial hypercholesterolemia (HoFH) often leads to premature coronary heart disease (CHD) as early as the second decade of life, with xanthomas typically developing during childhood. Several diagnostic tools exist for FH, with the Dutch Lipid Clinic Network Score (DLCNS) [6]being widely used to classify cases as probable or definite based on clinical features. This scoring system considers multiple factors, including family history of early cardiovascular disease (CVD), the individual's CVD history, untreated LDL-C levels, and physical signs such as tendon xanthomas or corneal arcus. The National Institute for Health and Clinical Excellence (NICE) recommends suspecting FH in individuals with elevated LDL-C and a family history of early-onset coronary disease, even in the absence of physical findings like xanthomas or corneal arcus, particularly in younger patients.[7]

Dutch Lipid Network Criteria for Diagnosis of FH	
Criteria	**Score**
Family history	
LDL >95th percentile in first-degree relative AND/OR	1
Premature CVD (men <55 y old, women <60 y old) in first-degree relative, OR	1
LDL >95th percentile in children <18 y old	2
Tendon xanthoma and/or arcus cornealis in first-degree relative, OR	2
Personal history	
Premature cerebral or peripheral vascular disease (men <55 y old, women <60 y old)	1
Premature CAD in patient (men <55 y old, women <60 y old)	2
Clinical Examination	
Arcus Cornealis at age <45	1
Tendon Xanthomas	6
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

Timely initiation of lifestyle modifications and lipid-lowering treatment is essential in the management of familial hypercholesterolemia (FH). For individuals with homozygous familial hypercholesterolemia (HoFH), treatment should be initiated promptly—preferably during infancy or immediately upon diagnosis. Management typically begins with ezetimibe alongside other cholesterol-lowering medications. Since achieving target LDL-C levels is particularly challenging in HoFH, lipoprotein apheresis is advised when accessible, ideally starting by the age of 5 and no later than 8 years. High-intensity statins combined with ezetimibe are preferred over statin monotherapy, though most patients require additional therapies to reach target LDL-C levels.[8] Within the first 8 weeks of treatment, the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors—such as evolocumab or alirocumab—should be considered, depending on availability. The effectiveness of PCSK9-targeted therapy depends on residual LDL receptor function. If an LDL-C reduction of more than 15% is observed, treatment may be continued; otherwise, discontinuation can be considered.[9] The therapeutic options for FH have expanded with the introduction of newer agents like inclisiran and bempedoic acid, either as standalone treatments or in combination with statins. Bempedoic acid acts upstream of statins by inhibiting adenosine triphosphate-citrate lyase, offering another pathway for reducing cholesterol synthesis.[10] Emerging therapies have expanded the treatment options for familial hypercholesterolemia (FH). Lomitapide, an oral microsomal triglyceride transfer protein (MTP) inhibitor, reduces the production of very low-density lipoproteins (VLDL), achieving up to a 60% reduction in LDL-C and approximately 15% reduction in Lp(a) over 26 weeks. Another novel agent, evinacumab—an ANGPTL3 monoclonal antibody—has shown efficacy in patients with homozygous FH aged 12 years and older. Administered

at 15 mg/kg intravenously every four weeks, it can reduce LDL-C levels by around 50% when added to maximally tolerated lipid-lowering therapies, with or without lipoprotein apheresis.[11] Lipoprotein apheresis (LA) remains a cornerstone treatment for both children and adults with HoFH and is typically performed biweekly or weekly.In the absence of LA, plasma exchange may serve as an alternative[12,13] In the presented case, the patient had a total cholesterol level of 183 mg/dL and an LDL-C of 496 mg/dL. Clinical findings included xanthelasmas, arcus cornealis, and a family history of premature coronary artery disease, all supported by abnormal lipid parameters. She experienced anginal symptoms over the preceding three months, and coronary angiography revealed triple vessel disease. A Dutch Lipid Clinic Network Score of 14 confirmed a definitive diagnosis of familial hypercholesterolemia. This case highlights the elevated risk of premature atherosclerotic cardiovascular disease (ASCVD) in FH patients. Early diagnosis and initiation of appropriate treatment, along with proactive family screening, are essential to halt disease progression and reduce cardiovascular risk.

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