International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Familial Hypercholesterolemia Manifesting as Hypertension in Young

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Abstract: ***This case report details the presentation and diagnosis of familial hypercholesterolemia (FH) in a 14-year-old girl who exhibited multiple xanthomas and persistent hypertension. Despite no family history of cardiovascular disorders, she presented with high blood pressure and characteristic skin lesions. Further investigations revealed hypercholesterolemia and a genetic mutation in the LDLR gene, confirming the diagnosis of FH. Treatment included statins and other medications to manage her cholesterol levels and blood pressure. The patient is under continuous follow-up, showing improvement in LDL levels and no development of hypertension-mediated organ damage. This case underscores the importance of considering FH in young patients with unexplained hypertension and xanthomas, highlighting the critical role of early diagnosis and intervention in preventing long-term cardiovascular complications.***

Keywords: familial hypercholesterolemia, hypertension in young

1. Introduction

Familial hypercholesterolemia is a common but undiagnosed disorder. It is characterized by elevated low density lipoprotein cholesterol which contributes to increased risk of cardiovascular events. This case reports a 14-year-old early adolescent female with no family history of cardiovascular disorders who presented with multiple xanthomas over the limbs for the past 02 years. Examination revealed a persistent BP > 140/90 mm Hg. Evaluation for secondary causes of hypertension in young, revealed hypercholesterolemia. Clinical exome sequencing revealed low density lipoprotein receptor (LDLR+) (autosomal recessive) pattern of familial hypercholesterolemia. This case report presents the differential of familial hypercholesterolemia to be considered as a cause of secondary hypertension.

2. Background

Familial hypercholesterolemia (FH) is common yet underdiagnosed autosomal dominant disorder that affects 1 in 220 individuals globally (1). FH is characterized by elevated low- density lipoprotein cholesterol (LDL-C) for whole life. It is associated with increased risks of early onset atherosclerosis cardiovascular events if not treated early. Mutations in the LDL-receptor gene, located on the short arm of chromosome 19, which causes a rise in LDL-C levels due to reduction in clearance of LDL-C which predisposes them to the development of atherosclerosis (2). This case report is about a 14-year-old female with multiple xanthomas who was incidentally found to have raised blood pressure with subsequent workup for hypertension in young revealing familial hypercholesterolemia.

3. Case presentation

14 years old early adolescent female presented with swellings over elbows, knees and ankles for 02 years. No h/o fever/ weight loss/ chronic cough. No h/o chest pain/ palpitation/ syncope/ headache/ blurring of vision/ projectile vomiting. no family history of diabetes mellitus, hypertension. On examination her BP was raised (> 140/100 mm hg) with presence of pallor. Dermatological examination revealed multiple non tender, papulo-nodular lesions over elbows, knees and tendoachilles region. Systemic examination revealed no abnormality. She was diagnosed as hypertension in young.

4. Investigations

Investigations revealed microcytic hypochromic anemia. Thyroid function test was normal. Evaluation for secondary causes of hypertension in young revealed hypercholesterolemia (Table 1). Hypertension mediated organ damage (HMOD) work up revealed ejection fraction (EF) 60%, no regional wall motion abnormality (RWMA), no MS/MR/AS/AR, no PE/clot/vegetations on 2D ECHO. Color doppler flow index (CDFI) carotid vessels revealed type III plaque (extending to a depth of 2.3 mm and length of 2.5 cm) in bilateral common carotid arteries with < 15% stenosis. Coronary angiography revealed non obstructive coronaries.Biopsy of papulo-nodular was suggestive of xanthoma. In view of multiple xanthomas and raised total

cholesterol and low-density lipoproteins, she was diagnosed as familial hypercholesterolemia. Clinical exome sequencing revealed LDLR + (autosomal recessive) variant of familial hypercholesterolemia [1].

5. Treatment

She was managed with tab atorvastatin 80 mg HS, tab ezetimibe 10 mg OD, tab amlodipine 10 mg OD and tab ecospirin 75 mg OD.

6. Outcome and follow-up

Patient is on follow-up on monthly basis in medical OPD. Her anti-hypertensives have been optimized based on blood pressure recordings. Latest lipid profile revealed reduction in LDL levels to 268 mg/dL. She has not developed hypertension mediated organ damage till date.

7. Discussion

Many patients with hyperlipidaemia have some combination of genetic predisposition (often polygenic) and medical or environmental contribution (medical condition, diet, lifestyle, or drug). Many, but not all, patients with hyperlipidaemia are at increased risk for ASCVD, which is the primary reason for making the diagnosis, as intervention can substantially reduce this risk. In addition, patients with severe hypertriglyceridemia may be at risk for acute pancreatitis and require intervention to reduce this risk. Primary Dyslipidaemias caused by single gene mutations can be divided into severe hypertriglyceridemia, hypercholesterolemia, mixed dyslipidaemia, hypolipidemic syndrome and primary low HDL cholesterol syndrome. There are many secondary factors often acting in concert with polygenic disposition. Some primarily affect triglycerides, some affect LDL-C and some influence both. FH is caused by mutations that lead to reduced function of the LDL receptor, with the most common being mutations in the *LDLR* gene itself. The reduction in LDL receptor activity in the liver results in a reduced rate of clearance of LDL from the circulation. The plasma level of LDL increases to a level such that the rate of LDL production equals the rate of LDL clearance by residual LDL receptor as well as non-LDL receptor mechanisms (3). Mutations in other genes such as PCSK9 and APOB also cause FH. Individuals with two mutated LDLR genes cause homozygous FH (HoFH) which has higher LDL-C as compared to mutations in one gene. Patients with HoFH usually are diagnosed based on hypercholesterolemia (LDL-C > 190 mg/dl) in absence of secondary aetiology and ideally with family history of hypercholesterolemia and/or premature ASCVD. Secondary causes such as nephrotic syndrome, obstructive liver disease and hypothyroidism should be ruled out. Young adulthood is a critical period when exposure to suboptimal BP or cholesterol is particularly harmful, and maintaining optimal levels of BP and LDL throughout young adulthood could yield substantial lifetime CVD prevention benefit (4). Cholesterol deposits within the skin of eyelids manifests as xanthomas and corneal deposits known as arcus senilis; those in connective tissues within and surrounding extensor tendons, especially the Achilles and extensor tendons of the hands, are called xanthomas. The most dangerous deposits occur within arteries, where they have potential to cause premature CAD, stroke and peripheral vascular disease (5). Atherosclerosis most commonly develops in aortic root, which can lead to valvular or supravalvular stenosis. 15% of patients with FH are hypertensive (6)**.** 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 (7). Extensor tendon xanthomas (typically Achilles, sub patellar, and hand extensor tendons) with extremely elevated LDL-C levels are considered specific for FH (8). Severe extensor tendon xanthomas have histological features that resemble foam cell formation and lipid accumulation in atherosclerotic plaques. Genetic testing offers additional insight regarding cardiac risks and diagnosis although the diagnosis of FH is still made clinically. Presence of FH mutation with same LDL-C levels as compared to individual harbouring no mutations confers significant higher cardiac risk (9)**.** There are no international recommended criteria for the diagnosis of FH. The main diagnostic tools being US Make Early Diagnosis to Prevent Early Death (MEDPED), UK Simon Broome system , the Dutch Lipid Network criteria, National lipid panel expert association and American Heart associations. Out of these only Dutch Lipid Network, UK Simon Broome system and AHA incorporate genetic testing as a diagnostic tool. As per CASCADE-FH registry, overall annualised ASCVD event rate was 2.21% with significant higher prevalence of hypertension and diabetes mellitus ($p< 0.01$) (10). Diagnosing FH in a child pave for cascade screening which involves testing of all first degree relatives for elevated LDL-C or a known genetic mutation. Diet and lifestyle modifications are the basis for LDL-C lowering in patients with FH, but multidrug treatment is often required to optimise LDL-C levels. ASCVD risk factors and other co-morbidities like type 2 diabetes mellitus and hypertension should be treated aggressively. American Heart Association (AHA recommends lipid lowering therapy when LDL-C > 190 mg/dl (11). A study revealed 76% reduction in cardiovascular events in statin treated patients as compared to placebo (12). Ezetimibe results in inhibition of cholesterol absorption. PCSK9 and ACL inhibitor can also be used as adjunctive therapy to reduce LDL-C.

8. Table

Table 1

INVESTIGATIONS	RESULT
Hb (g/dL)/MCV	8.5/59.7
TLC (/cumm)/ DLC (N/L/M/E)	6760/ 44/42/9/4
PBS	Microcytic hypochromic RBCs mixed with normocytic normochromic RBC, pencil cells and tear drop cells. Mentzer index: 12.72
Platelets (/cumm)	2.53
Urea/Cr (mg/dL)	18/0.5
Na/K (mEq/L)	141/4.6
T.Bil/ D.Bil (mg/dL)	0.6/0.1
T.Protein/ Alb/ Glob (mg/dL)	8.4/3.6/4.8
AST/ALT (IU/L)	23/22
PT/INR/aPTT	14.6/1.06/32.1
Iron/ TIBC/ Ferritin (mg/dL/ mg/dL/ ng/mL)	13/459/7.27

T.Chol/TG/HDL/LDL (mg/dL)	517/130/28/463
Blood Glucose F/PP (mg/dL)	99/137
T3/T4/TSH (ng/mL/ mcg/dL/ microIU/mL)	1.49/7.55/3.74
CPK (IU/L)	50
2D ECHO	LVEF 60% Sinus solitus Levocardia Concordant, normal systemic and pulmonary vessels, IAS/ IVS intact, no MS/MR/AS/AR.
USG Abdomen and KUB with CDFI renal vessels	Liver 14.1 cm, no evidence of fatty liver. RK 9.2 cm, LK 9.4 cm. RI in segmental and subsegmental arteries (0.72-0.78)
CDFI Neck vessels	Bilateral CCA (proximal) type III plaque with no significant stenosis (extending to a depth of 2.3 mm and length of 2.5 cm. it is circumferential and causing a stenosis of <15%
HPE Right Elbow	Consistent with xanthoma
NGS	Heterozygous mutation familial hypercholesterolemia-1 (Gene: LDLR+) on exon 7 and 11

9. Figures

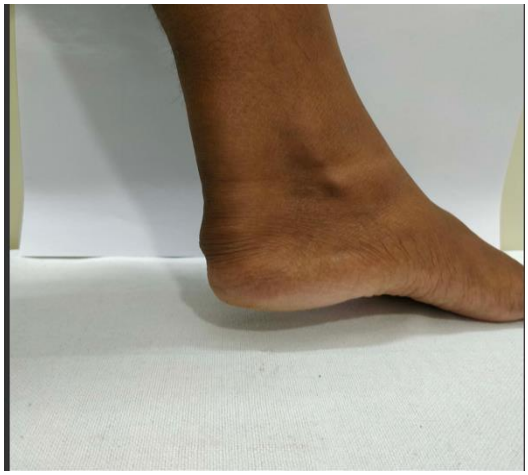

Image 1: Xanthoma at ankle

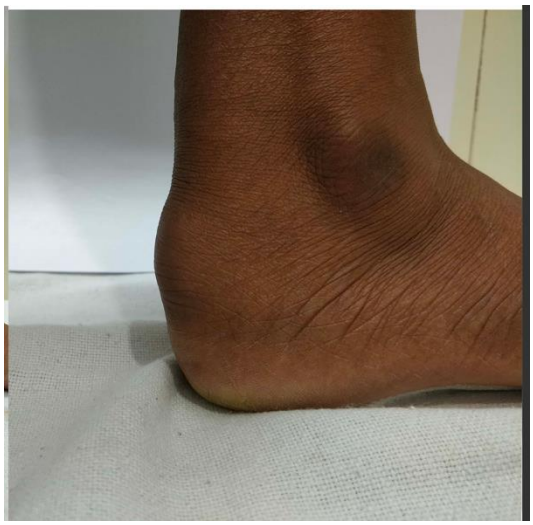

Image 2: Xanthoma at ankle

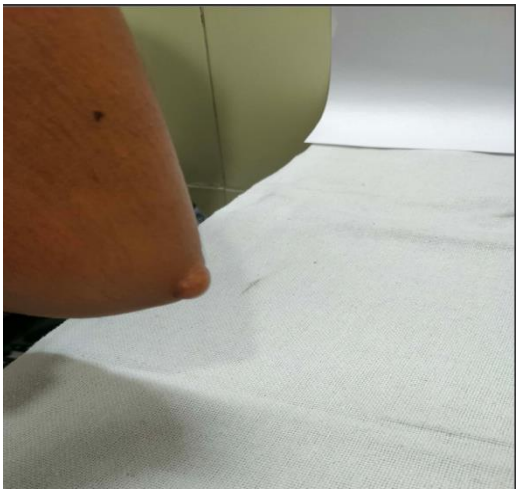

Image 3: Xanthoma at elbow

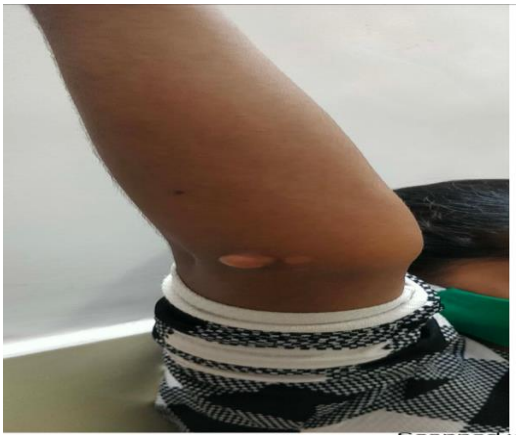

Image 4: Xanthoma at elbow

Image 5: Xanthoma at elbow

Image 6: Xanthoms at DIP joint

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