International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2019): 7.583

Familial Hypercholesterolemia: Case Report

Dr Pritish Ingole, Dr Ajeya Ukadgaonkar, Dr Ashish Deshpande

Abstract: ***The following report is of a patient who came for a routine OPD visit with complaint of breathlessness on exertion. On thorough clinical examination the patient had distinct featuressuch as - Presence of xanthelasma, corneal arcus, multiple tuberous xanthomas present bilaterally over shoulder joints, elbow joints, buttocks and knee joints. Serum cholesterol levels were highly raised. Coronary angiography revealed calcified coronaries with triple vessel involvement. The patient had LV dysfunction. Genetic testing and skin biopsy was also done. The patient was discharged on optimal medical management.***

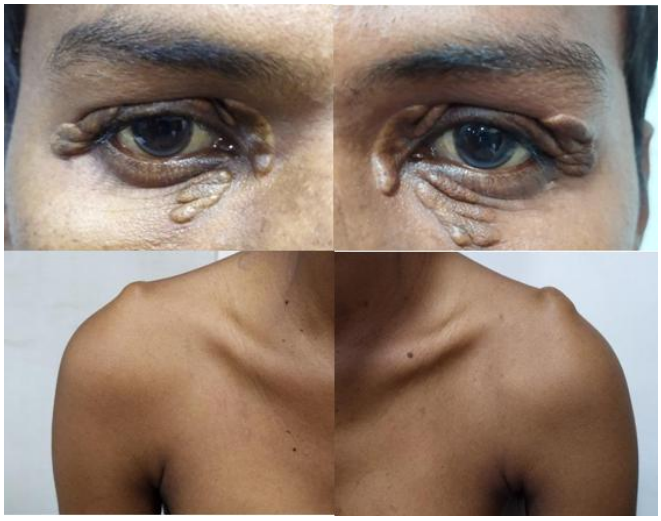
Keywords: Familial Hypercholesterolemia, OPD, exertion, xanthelasma, corneal arcus

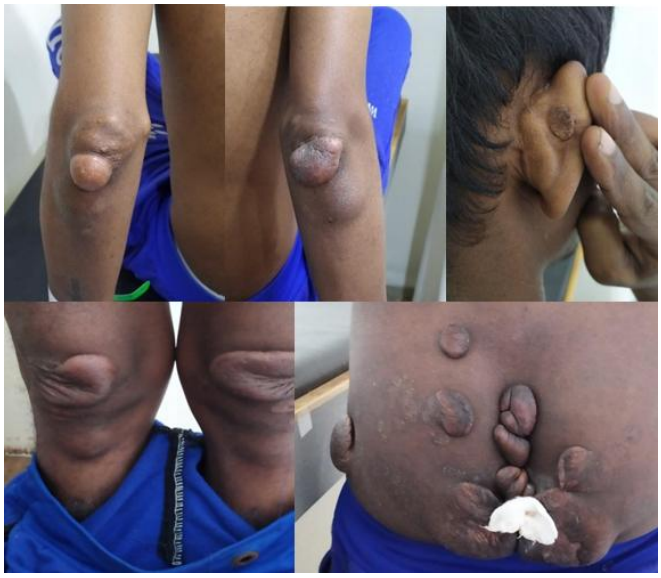
1. Case Report

Mr. Manish Hardekar was a 30-year-old man, Hindu by religion, shopkeeper by profession, residing in the Jalna district of Maharashtra, India. Born of a consanguineous marriage, Mr. Hardekar came to the OPD with a complaint of breathlessness on exertion since the last 3 months. Initially breathlessness was restricted to non-accustomed activities, but over the period of 3 months the conditions worsened and he felt breathless even at rest. He also reported intermittent retrosternal chest pain which radiates towards the back. Although such did not last for more than 2 minutes, and were relieved with rest, they indeed were exertional in nature. The patient had no addictive behavior.The patient had no history of diabetes, hypertension, or any significant medical or surgical illness. There was also no family history of ischemic heart disease (IHD) or death due to cardiac disorders.

On general examination the pulse was 90/min, regular, normal in character, and normal in amplitude with no radio-radial or radio-femoral delay. Blood pressure was 110/70 mm Hg in the right arm in supine position and 108/70 mm Hg in standing position. There was mild pallor, with no clubbing/cyanosis or lymphadenopathy.

- The distinct features presented by the patient are as follows- Presence of xanthelasma, corneal arcus, multiple tuberous xanthomas present bilaterally over shoulder joints, elbow joints, buttocks and knee joints.





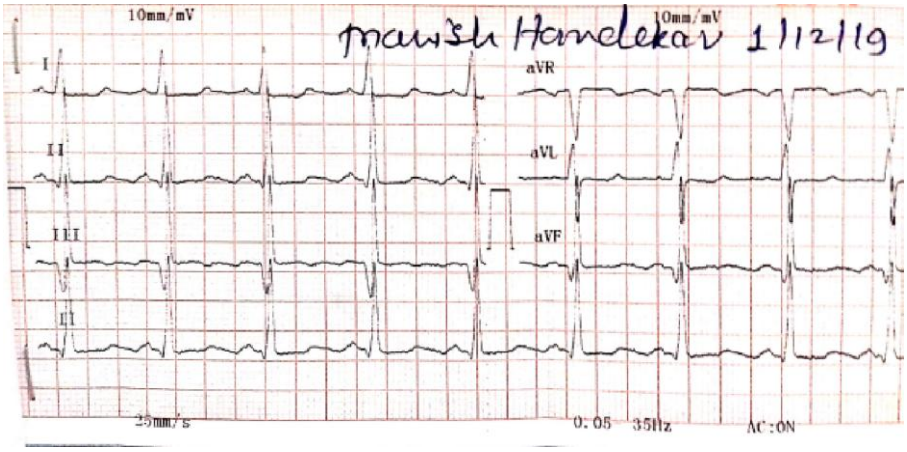
On cardiovascular systemic examination,

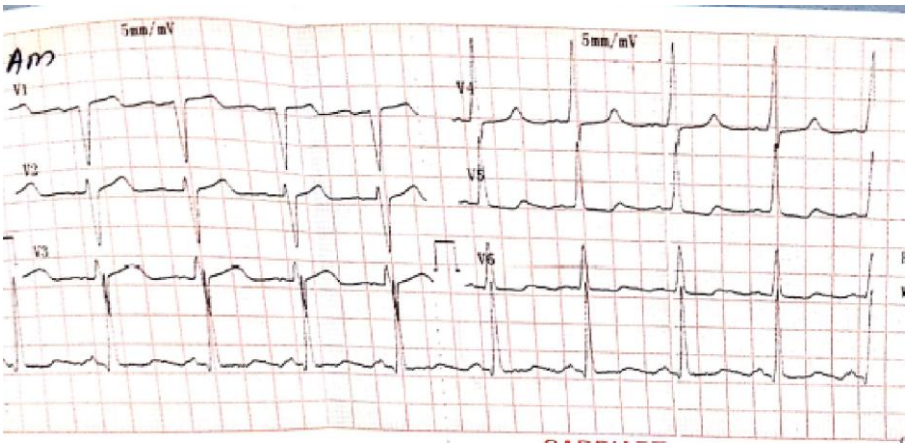
- Jugular venous pressure (JVP) was normal.
- Apex beat was present in left 6th intercostal space in anterior axillary line, ill sustained and diffuse.
- Heart sounds were normal.

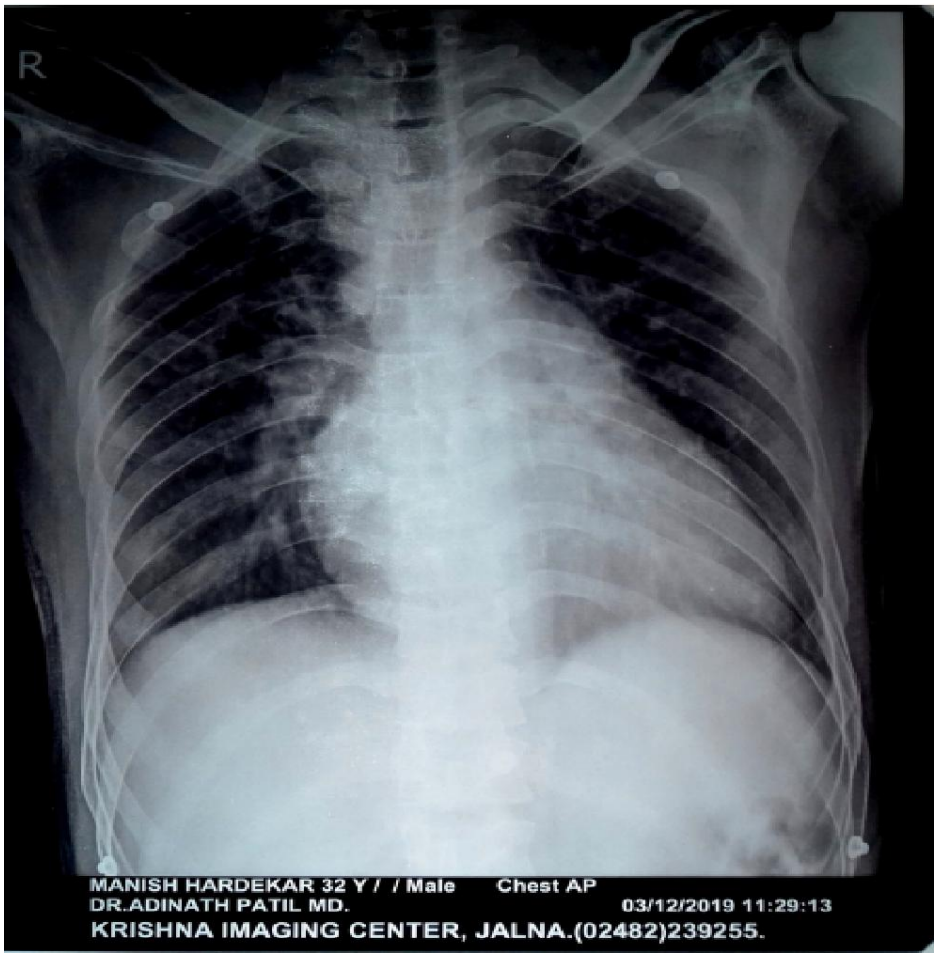
Examination of other systems was essentially within the normal limits. On blood investigations,

- Hemogram and routine urine examination was within normal limits.
- Thyroid function tests, liver function tests and kidney function tests were within normal limits.
- Lipid profile revealed the total cholesterol level to be 698 mg/dL. High density lipoprotein (HDL) level was 28 mg/dL and the level of serum triglyceride was 124 mg/dL.

ECG and Chest X-ray were as follows:







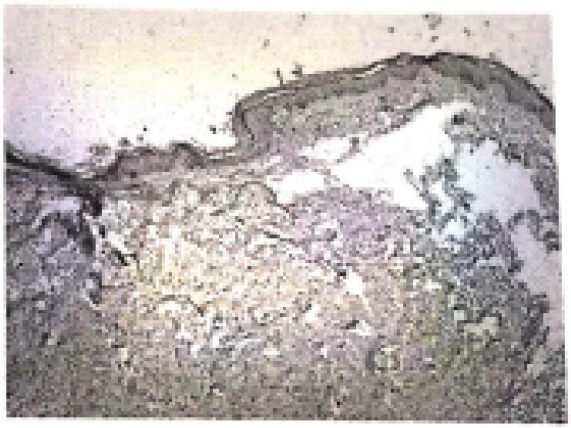
2D Echocardiography and colour doppler revealed,

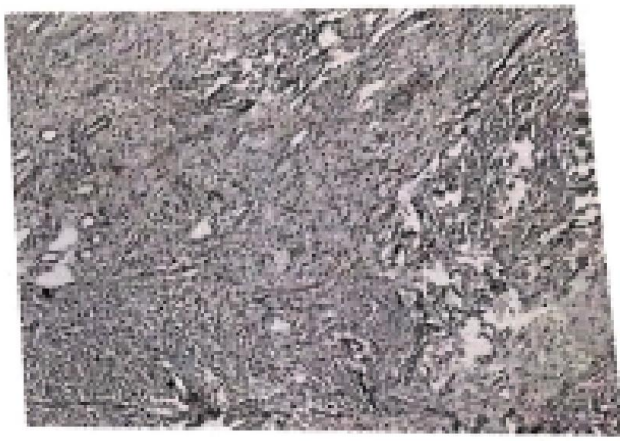
- The left ventricle was dilated.
- Global left ventricular hypokinesia which was more in the anterior segments.
- The left ventricular systolic function was severely compromised. The ejection fraction was 20-25%.
- Calcified and thickened aortic valve.
- Moderate mitral regurgitation.
- No pulmonary hypertension.

Coronary Angiography revealed-

- Triple vessel coronary artery disease (Diffusely diseased and calcified vessels).

Skin biopsy confirmed the lesions to be tuberous xanthomas.





Genetic testing revealed the presence of the gene pathogenic for Familial hypercholesterolemia-1

RESULTS

LIKELY PATHOGENIC COPY NUMBER VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS IDENTIFIED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***LDLR* [+]** (ENST00000558518.1)	Exon 12	c.(1705+1_1706-1)_(1845+1_1846-1)del (**Exonic deletion**)	Homozygous	Familial hypercholesterolemia -1	Autosomal dominant	Likely Pathogenic

[$]Genetic test results are reported based on the recommendations of American College of Medical Genetics [1].

2. Discussion

Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterised by increased levels of total cholesterol and low-density lipoprotein (LDL) [1, 2, 3]. FH remains associated with a high risk for premature coronary artery disease (CAD). FH is a disorder of absent or grossly malfunctioning low-density lipoprotein (LDL) receptors. The LDL receptor gene is located on the short arm of chromosome 19. It is the primary determinant of hepatic LDL uptake, which normally processes approximately 70 % of circulating LDL. Goldstein and Brown discovered the LDL receptor and determined that FH was caused by an autosomal dominant mutation [14, 15], with 79 % of them being expressed as a hypercholesterolemic phenotype. Defects in the genes encoding apo B and proproteinconvertasesubtilisin/kexin type 9 (PCSK9) are responsible for approximately 5% and less than 1% of the FH cases, respectively [13].LDL receptor function varies from nonexistent up to about 25% of normal receptor activity [16].

The inheritance pattern for the FH gene is the same for males and females. The consequences of a defective LDL receptor and subsequent elevations of LDL are present at birth, but age is relevant because the longer patients live with extremely elevated LDL levels, the higher is the risk of developing a CAD.

Early detection and implementation of aggressive management strategies to lower the LDL levels help prevent or slow down the progression of coronary atherosclerosis

Signs and Symptoms

Patients with homozygous FH show following features:

1. Symptoms consistent with ischemic heart disease, peripheral vascular disease, cerebrovascular disease, or aortic stenosis.
2. Articular symptoms such as tendonitis or arthralgias.
3. Unusual skin lesions, such as cutaneous xanthomas at birth or by early childhood (eg, planar xanthomas, tuberous xanthomas; later, tendon xanthomas)
4. Corneal arcus may be present and is sometimes circumferential.
5. Murmur of aortic stenosis may be present.

Most patients with homozygous FH do not survive adulthood beyond age 30 years unless treated with unusual methods, such as liver transplantation, LDL apheresis, or ileal bypass surgery to dramatically lower their LDL levels.
Patients with heterozygous FH show following features-

Signs and symptoms of heterozygous FH in adults include the following:

- Long-standing history of severe hypercholesterolemia dating back to childhood.
- If no previous acute coronary event, symptoms consistent with ischemic heart disease, especially in the presence of other cardiovascular risk factors (especially smoking).
- Past or present symptoms of recurrent Achilles tendonitis or arthritis.

Children with heterozygous FH do not have symptoms related to coronary heart disease (CHD), and most of them do not develop tendon xanthomas or corneal arcus. However, one parent will have severe hypercholesterolemia and will probably have either a personal or family history for premature coronary artery disease.

Diagnosis

In absence of secondary causes of hypercholesterolemia, the diagnosis of both homozygous and heterozygous FH is based primarily on assessing the increase in LDL levels.

A probable diagnosis of heterozygous FH can be made if the LDL level is greater than 330 mg/dL. Definitive diagnosis can be made only with gene or receptor analysis.

However, a substantial increase in serum triglyceride levels also indicates the possibility of another lipid disorder.

Findings on lipid analysis in patients with FH include the following:

- Homozygous FH: Severely elevated cholesterol levels (total cholesterol and LDL levels >600 mg/dL); triglyceride levels within the reference range.
- Heterozygous FH: Elevated LDL levels, commonly >250 mg/dL; in patients younger than 20 years, an LDL level higher than 200 mg/dL is highly suggestive of heterozygous FH.
- LDL receptor analysis can be used to identify a specific LDL receptor defect, and LDL receptor or apoB-100 studies can help distinguish heterozygous FH from the similar syndrome of familial defective apoB-100.

In August 2013, the European Atherosclerosis Society (EAS) published a consensus statement for screening and treatment of heterozygous FH [4, 5]. The recommendations for screening for heterozygous FH include patients with:

- A family member presenting with diagnosed FH;
- Plasma cholesterol in an adult ≥8mmol/L (≥310 mg/dL);
- Plasma cholesterol in a child ≥6mmol/L (≥230 mg/dL);
- Premature CHD;
- Tendon xanthomas; or
- Sudden premature cardiac death.

Management

The goal of FH treatment is to reduce the risk of CHD or risk of a CHD-equivalent condition such as carotid artery disease, diabetes, and peripheral arterial disease [6, 7, 8].

Homozygous FH

The following are used in the management of homozygous FH:

- Lifestyle changes: Recommended for cardiovascular benefits [9, 10].
- High doses of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) combined with bile acid sequestrants, ezetimibe, and niacin [11]
- Anti–proproteinconvertasesubtilisin/kexin type 9 (anti-PCSK9). Monoclonal antibodies (specifically, evolocumab and alirocumab) can be used as an adjunct to diet and maximally tolerated statin therapy [12], or Mipomersen, or Lomitapide.
- Estrogen replacement therapy in postmenopausal women.
- LDL apheresis for selective removal of lipoproteins that contain apo-B (when the LDL receptors are absent or non functional).
- The following are procedures used in the treatment of homozygous FH:
- Portacaval anastomosis
- Liver transplantation (rarely)

Investigative therapies for homozygous and heterozygous FH include probucol, which causes regression of cutaneous and tendon xanthomas in patients with both homozygous and heterozygous FH but no long-term benefits for reduced coronary atherosclerosis, and gene therapy.

Heterozygous FH

The following are used in the management of heterozygous FH:

- Lifestyle modification, including diet (limited saturated fats, trans fats, and cholesterol); weight management; aerobic/toning exercises
- HMG-CoA reductase inhibitors (statins) (eg, simvastatin, atorvastatin, or rosuvastatin), and one or more other LDL lowering medications, or
- Adenosine triphosphate-citrate lyase (ACL) inhibitor (eg, bempedoic acid) added to maximally tolerated statin therapy, or
- Bile acid sequestrants, or
- Ezetimibe, or
- Niacin
- Estrogen replacement therapy in postmenopausal women.

LDL apheresis can be considered for the following patients:

- CHD patients for whom conventional therapies fail to lower the LDL level below 200 mg/dL.
- Those without CHD but have an LDL level greater than 300 mg/dL.

References

[1] Illingworth DR, Duell PB, Connor WE. Disorders of lipid metabolism. Felig P, Baxter JD, Frohmin LA, eds. Endocrinology and Metabolism. 1315-1403.
[2] Ueda M. Familial hypercholesterolemia. Mol Genet Metab. 2005 Dec. 86 (4):423-6. [Medline].
[3] Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003 May. 168 (1):1-14. [Medline].
[4] Wood S. New EAS Consensus Document Tackles Familial Hypercholesterolemia. Medscape Medical News. Available at http://www.medscape.com/viewarticle/805252. Accessed: September 5, 2013.
[5] Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. 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. Eur Heart J. 2013 Aug 15. [Medline].
[6] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16. 285 (19):2486-97. [Medline].
[7] National Cholesterol Education Program Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The Expert Panel. Arch Intern Med. 1988 Jan. 148 (1):36-69. [Medline].
[8] Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13. 110 (2):227-39. [Medline].
[9] Connor WE, Connor SL. Dietary treatment of familial hypercholesterolemia. Arteriosclerosis. 1989 Jan-Feb. 9 (1 Suppl):I91-105. [Medline].
[10] Illingworth DR. Management of hypercholesterolemia. Med Clin North Am. 2000 Jan. 84 (1):23-42. [Medline].
[11] Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001 Nov 29. 345 (22):1583-92. [Medline].
[12] Toklu B, Amirian J, Giugliano RP. Current indications, cost, and clinical use of anti-PCSK9 monoclonal antibodies. American College of Cardiology. Available at http://www.acc.org/latest-in-cardiology/articles/2016/05/18/14/34/current-indications-cost-and-clinical-use-of-anti-pcsk9-monoclonal-antibodies. May 19, 2016; Accessed: July 10, 2016.
[13] WiegmanA et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015 Sep 21. 36 (36):2425-37. [Medline]. [Full Text].
[14] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16. 285 (19):2486-97. [Medline].
[15] National Cholesterol Education Program Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The Expert Panel. Arch Intern Med. 1988 Jan. 148 (1):36-69. [Medline].
[16] Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13. 110 (2):227-39. [Medline]