Acute Coronary Syndrome in an Adolescent with Homozygous Familial Hypercholesterolemia

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ABSTRACT

Introduction: Familial hypercholesterolemia is a single gene disorder with autosomal codominant pattern of inheritance. While heterozygous familial hypercholesterolemia is common, homozygous familial hypercholesterolemia is distinctly uncommon with a worldwide prevalence of 1 in 1 million persons.
Case report: Here we report a boy of 15 years of age, who had xanthomas, xanthelasmas and presented to us with acute coronary syndrome. His paternal uncle had died prematurely of coronary artery disease. The patient had very high level of LDL-C in blood. Coronary angiography revealed left main coronary artery stenosis with involvement of other coronaries.
Conclusion: Very few cases of familial hypercholesterolemia have been reported from India. This is more likely due to lack of awareness of the disease rather than due to its rarity. Early diagnosis and prompt treatment will help prevent life threatening complications like premature atherosclerosis.

Keywords: Familial Hypercholesterolemia, Xanthomas, Premature Atherosclerosis.

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated level of low density lipoprotein cholesterol (LDL-C), tendinous xanthomas and premature coronary atherosclerosis It is an autosomal codominant disorder characterized by gene dose defect, in that the individuals with two mutant LDL receptor alleles (FH homozygotes) are much more affected than those with one mutant allele (FH heterozygotes).[1]
FH is one of the commonest inherited disorders, with an estimated worldwide prevalence of 1 in 500 (heterozygotes).[2] The homozygous state is rare with a prevalence of one in million persons. These prevalences likely represent underestimates. The patients of FH are at high risk of developing coronary artery disease and sudden death, unless the condition is recognized and treated promptly. Here, we report a case of homozygous FH in an adolescent who presented with acute syndrome.

CASE REPORT

A fifteen year old boy, born of nonconsanguineous marriage, presented with severe chest pain of 5 days duration. The pain was typical of angina. The boy had 1 brother and 2 sisters. None of the siblings suffered from coronary artery disease (CAD). The parents were also doing well. However, one paternal uncle had died of acute myocardial infarction at the age of 38 years.
Hemodynamically he was stable. Cutaneous examination revealed multiple and extensive tendinous xanthomas of varying size (1-10 cm), distributed over axilla, elbows, hands, knees and feet. (Fig.1-4).
Xanthelasmas were present around the eyelids and the eyes showed corneal arcus (Fig 3). Examination of dorsum of hands revealed characteristic involvement of interdigital spaces showing pathognomonic intertriginous xanthomas (Fig 2). The patients parents had noticed xanthomas in the patient since 5 years of age. The ECG showed significant ST segment depression in anterior precordial leads with ST segment elevation in lead aVR. The troponin level was not elevated. A diagnosis of acute coronary syndrome was made. The echocardiographic examination was normal.
Routine laboratory parameters like Hb%, DC, TLC, blood sugar, serum urea, creatinine thyroid function tests and liver function tests were normal. Lipid profile of the patient demonstrated LDL-C to be very high with normal triglyceride level (Table 1). Lipid profile of the parents and siblings were done. Both the parents and 1 brother had very high serum LDL-C level. Coronary angiogram was done on the next day which revealed left main coronary artery stenosis and involvement of other coronary arteries as well. (Fig 5,6)
A final diagnosis of familial hypercholesterolemia with acute coronary syndrome was made. The patient was immediately sent to cardiothoracic surgery department for coronary artery bypass surgery because of significant left main coronary artery involvement. In the meantime, he was put on high dose statin (Atorvastatin 80 mg/day) along with anti-ischemic agents. The diagnosis of familial hypercholesterolemia was made in this case as per the Dutch Lipid Clinic

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How to cite this article: Biswajit Das, Trinath Kumar Mishra. Acute coronary syndrome in an adolescent with homozygous familial hypercholesterolemia. International Journal of Contemporary Medical Research 2016;3 (1):312-314.

	Total cholesterol (mg/dl)	LDL –C (mg/dl)	TG (mg/dl)	HDL (mg/dl)
Patient	1080	923	168	40
Father	389	281	159	43
Mother	413	295	160	38
Brother	390	267	138	44
Eldest sister	197	106	145	45
Elder sister	401	308	156	37

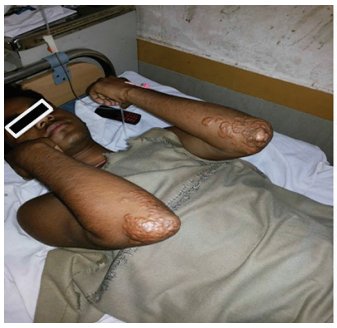
Table 1: Lipid profile of the patient and the family members

Group 1: Family history	**Points**
(i) First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease (CHD) OR	1
(ii) First-degree relative with known LDL cholesterol >95th percentile by age and gender for country OR	1
(iii) First-degree relative with tendon xanthoma and/or corneal arcus OR	2
(iv) Child(ren) <18 years with LDL cholesterol >95th percentile by age and gender for country	2
Group 2: clinical history	
(i) Subject has premature (<55 years, men; <60 years, women) CHD	2
(ii) Subject has premature (<55 years, men;<60 years, women) cerebral or peripheral vascular disease	1
Group 3: physical examination	
(i) Tendon xanthoma	6
(ii) Corneal arcus in a person,<45 years	4
Group 4: biochemical results (LDL cholesterol)	
>8.5 mmol/L (>325 mg/dL)	8
6.5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
Group 5: molecular genetic testing (DNA analysis)	
(i) Causative mutation shown in the LDLR, APOB, or PCSK9 Genes	8
A 'definite FH' diagnosis can be made if the subject scores .8 points. A 'probable FH' diagnosis can be made if the subject scores 6 to 8 points. A 'possible FH' diagnosis can be made if the subject scores 3 to 5 points. An 'unlikely FH' diagnosis can be made if the subject scores 0 to 2 points. Use of the diagnostic algorithm: per group only one score, the highest applicable, can be chosen. For example, when coronary heart disease and tendon xanthoma as well as dyslipidaemia are present in a family, the highest score for family history is 2. However, if persons with elevated LDL cholesterol levels as well as premature coronary heart disease are present in a family, but no xanthoma or children with elevated LDL cholesterol levels or a causative mutation are found, then the highest score for family history remains 1.	

Table-2: Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolemia in adults

Network Criteria. (Table 2)[3]

A diagnosis of homozygous familial hypercholesterolemia was made because of of significant left main coronary artery involvement. In the meantime, he was put on high dose statin (Atorvastatin 80 mg/day) along with anti-ischemic agents.



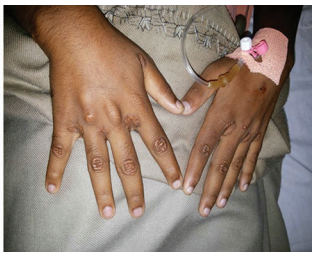
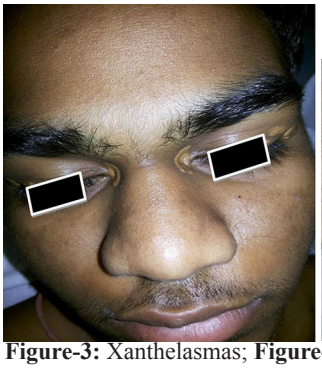


Figure-1: Xanthomas over the elbows; **Figure-2:** Intertriginous xanthomas



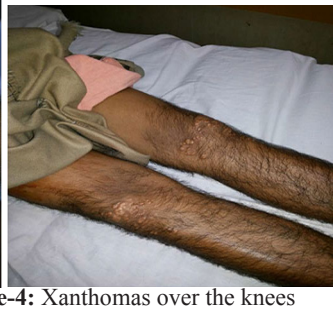
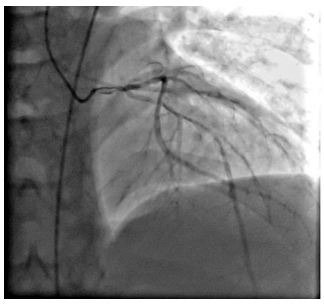


Figure-3: Xanthelasmas; **Figure-4:** Xanthomas over the knees



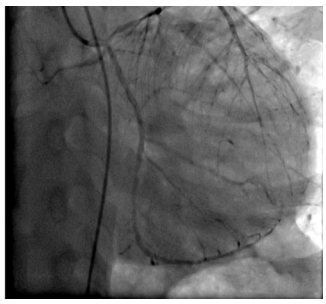


Figure-5: CAG (AP cranial view) showing involvement of Left main and LAD & LCX; **Figure-6:** CAG (AP caudal view) showing involvement of Left main and LAD & LCX

DISCUSSION

Familial hypercholesterolemia is one of the commonest inherited disorder, though the frequency is considerably higher in some populations because of a founder effect. There is no true estimate of people diagnosed with familial hypercholesterolemia in India. Patients coming to hospitals are screened for their cholesterol levels only without any emphasis on the diagnosis of familial hypercholesterolemia. In western countries, definite criteria for FH have been laid down and cascade screening is routinely done to diagnose FH.[3] Reports of homozygous FH are still rare from India and only few cases have been reported. Scant reports may have been due to lack of awareness of the disorder as Indians migrated and settled in Africa have an increased frequency of FH.[7]

The pedigree of the family has been depicted in the figure. Though FH is an autosomal codominant disorder, exogenous factors like environmental, metabolic, and genetic factors influence the clinical phenotype.[2] This explains absence of CAD in parents and siblings of the index patient despite having significant elevation of LDL-C level. Familial hypercholesterolemia or Fredricksons type IIa hyperlipoproteinemia is an autosomal dominant disorder caused by >900 mutations in the LDL receptor gene present on chromosome 19, leading to lack of functional LDL receptors on the cell surface.[1] This causes decreased uptake of LDL into the cells, particularly into the liver, from the blood, resulting in increased LDL-C.

While FH in heterozygous state has a prevalence of 1 in 500 individuals, homozygous FH is very rare with a prevalence of 1 in 1 million persons.[2] LDL-C is removed from the plasma in heterozygous state at two- third of normal rate, resulting in two- three fold elevation of LDL-C. In homozygous state it is removed at one- third of the normal rate resulting in 6-8 fold elevation of plasma LDL-C.[5] Our patient of homozygous FH had LDL-C level of 926 mg/dl. Homozygous FH patients develop xanthomas before the first decade of life. Patients have multiple types of xanthomata, including tuberous, subperiosteal, tendon xanthomas, elevated xanthomatous plaques.[8] Our patient had all these forms of xanthomata. Besides, he had intertriginous xanthomas in the web spaces of fingers, which is characteristic of homozygous FH. These xanthomas develop because lipid leakage from the vessel into the surrounding tissues, where macrophages subsequently phagocytose these lipids. The cholesterol is not degraded, which accumulates in these cells, giving rise to foamy macrophages. Familial hypercholesterolemia is a common genetic disorder of premature coronary namely acute myocardial infarction and angina, due to lifelong elevated LDL-C If levels.[9] left untreated heterozygous FH patients develop CAD before age 55, while homozygous patients typically develop CAD very early and if left untreated die before age 20.[3] Our patient of homozygous FH was 15 had already developed left main coronary artery stenosis, with involvement of other coronary arteries leading to acute coronary syndrome. While the immediate attention of such patients is to revascularise the coronary arteries, long term therapy includes lifestyle modification including dietary restriction and physical activity.[10] Cholesterol lowering drugs should be initiated immediately which includes high dose statins, ezetimibe, and bile acid binding resins. In homozygous FH cases, lipoprotein aphaeresis is often necessary, which is conducted only in specialised lipid clinics.

CONCLUSION

We report a case of homozygous familial hypercholesterolemia with severe premature atherosclerosis. coronary arteries Despite huge medical advancement, FH is frequently under diagnosed, with a delay in diagnosis of FH is important for the patient and also has serious implications for the family members who inherit the same disorder. Early diagnosis and prompt institution of therapy to lower the serum LDL-C level will prevent the patient from developing premature atherosclerosis.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 07-12-2015; **Published online**: 28-12-2015