Familial hypercholesterolemia

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ABSTRACT

Familial homozygous hypercholesterolemia is a rare autosomal disorder characterized by high levels of cholesterol, extensive tendon xanthomatosis and premature development of atherosclerotic disease. Early coronary artery disease with myocardial infarctions and sudden deaths are common. We reported a family of familial hypercholesterolemia from the Kashmir valley of the Indian subcontinent. The appearance and the severity of the cutaneous xanthomas was found to be age related suggesting a role for the duration of hypercholesterolemia in the development of xanthomatosis.

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Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by an elevated level of plasma low density lipoprotein cholesterol (LDL-CH), tendon xanthomas, and premature atherosclerosis. The genetic basis of FH is the lack of functional receptors for LDL-CH on the cell surface.[1] The heterozygous form of FH is estimated to be 0.2% in most populations.[1] However, in selected populations, such as Afrikaners of South Africa[2] and French Canadians,[3] the frequency of FH is much higher due to a founder effect. In European and North American populations homozygous FH is extremely rare, being estimated to occur in approximately one in one million births.[1] Homozygous FH is characterized by a marked elevation of LDL-CH, cutaneous as well as tendon xanthomas, arcus cornealis, and generalized atherosclerosis, which develops during childhood. Total cholesterol levels often exceed 500 mg/dl and can be as high as 1200 mg/dl (normal 140-200 mg/dl).[4] If untreated, death from myocardial infarction or sudden cardiac death is expected to occur by the end of the third decade of life.[1] Herein, we report a 14-year-old boy with homozygous FH. In this study, we reported a family of familial hypercholesterolemia with premature involvement of cardiovascular system by eary atherosclerosis indicated by the appearance of xanthomas as the age advances.

Case Report. A 14-year-old boy, born of a consanguineous marriage presented with multiple painless swellings over his hands, elbows, buttocks, knees and feet that progressively increased in size for the past 3-4 years. There was an accompanying orthopnea and paroxysmal nocturnal dyspnea of one-month duration with episodic chest pain. Clinical examination of the patient revealed a thin built patient (body mass index = 14), with multiple, firm, xanthomatous swellings (tuberous, tendon, eruptive and planar), each measuring 2-3 cm in size over hands (extensor tendons and interdigital areas), elbows, buttocks, knees and feet (**Figures 1-3**). Pertinent findings revealed a cardiomegaly and a grade 2-3 systolic murmur at mitral area with a S3 gallop. The rest of the examination was normal. The patient's sister (aged 9 years) and younger brother (aged 6 years) had also developed similar nodular swellings over multiple areas of the body over the past few years but both were otherwise asymptomatic. The patient's father, mother and another younger sister (aged 18 months) were asymptomatic and without any swellings. Examination of the siblings revealed similar cutaneous swellings with normal systemic examination.

Hemogram, routine biochemical parameters, and thyroid hormones were normal. The lipidograms of the patient and the family members is depicted in **Table 1**. The lactate dehydrogenase (LDH) was 1246 U/l (normal 240 -430 IU/l). Electrocardiogram revealed left ventricular hypertrophy with ischemic changes in lateral chest leads. Echocardiography revealed features suggestive of dilated cardiomyopathy with an ejection fraction of 29%, moderate mitral regurgitation, mild aortic regurgitation, with calcified annulus. Biopsy of the skin lesions revealed deposition of foamy histiocytes in the dermis. The patient was scheduled for a coronary

angiography, which he wanted at a later date due to a social function. He went home and a week later was reported dead after an episode of breathlessness and chest pain.

Discussion. Our patient with all his siblings constitutes the first family of homozygous FH reported from our part of the country. The familial clustering, siblings exhibiting xanthomas, premature coronary artery disease (CAD) and hypercholesterolemia suggest a diagnosis of homozygous hypercholesterolemia. Homozygous FH causes widespread atherosclerosis in all of the major arterial beds including the carotids, coronaries, femoral and iliac vessels. Children are at risk for extremely early coronary events, sudden death or myocardial infarction that may occur as early as 1-2 years. Untreated survival beyond young adulthood is unlikely.[4] Our index patient had features suggestive of an ischemic cardiomyopathy but did not live long for any further coronary workup.

Earlier reports of familial homozygous hypercholesterolemia have also demonstrated the development of various types of xanthomas, early aortic stenosis and CAD in these patients.[5] In a Japanese database of patients with FH, the clinical features and the frequencies of accompanying vascular diseases in 660 cases of FH homozygotes and heterozygotes showed that the incidence of CAD was negatively associated with plasma high density lipoprotein-cholesterol (HDL-CH) levels, but not with plasma LDL-CH levels. Risk factor analysis revealed that hypertension, male gender, smoking, low HDL-cholesterol levels, age >50 years, existence of diabetes mellitus, and hypertriglyceridemia were positive risk factors for CAD.[6] A family of 3 sisters was reported from Berlin, with autosomal recessive inheritance has been reported with phenotypic homozygous hypercholesterolemia with massive tuberous xanthomas over knees, elbows, buttocks and thighs.[7] Our patient and his siblings also had extensive xanthomatosis. The existence of various types of xanthomas including planar, tuberous, tendinous and planar xanthomas (on hands, elbows, buttocks or knees) are considered diagnostic for a homozygous state in our patient and are distinct from other xanthomas as ejection fraction of their yellow-orange colour. The siblings of our patient had xanthomas in various stages of developmental appearance and severity chronologically related to the age of the subjects. This strongly suggests that the duration of hypercholesterolemia is a key factor in the development and severity of xanthomas. Our family is probably the first to demonstrate a chronologically related development and severity of the extent of xanthomatosis. Other investigators from other countries have also reported extensive xanthomatosis as a consistent finding with a variable frequency of the development of CAD,[8,9] sudden death being one of the manifestations.

At the molecular level, FH is a heterogeneous disorder; more than 200 mutations of the LDL receptor gene having been reported so far[1,10-12] and in some cases the effect of these mutations on LDL receptor function has been fully characterized.[10,11] These receptor defects have been grouped into 5 major classes: 1. failure to express receptor protein synthesis; 2. defective transport

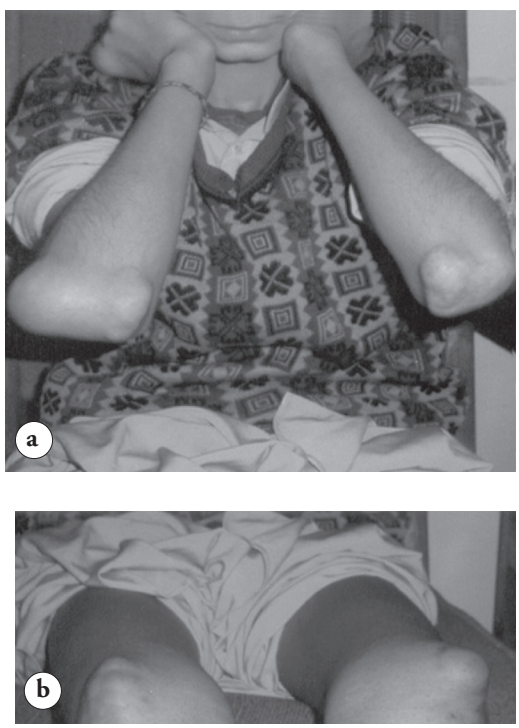

Figure 1 - Index case with xanthomas a) elbow xanthomas b) knee xanthomas.

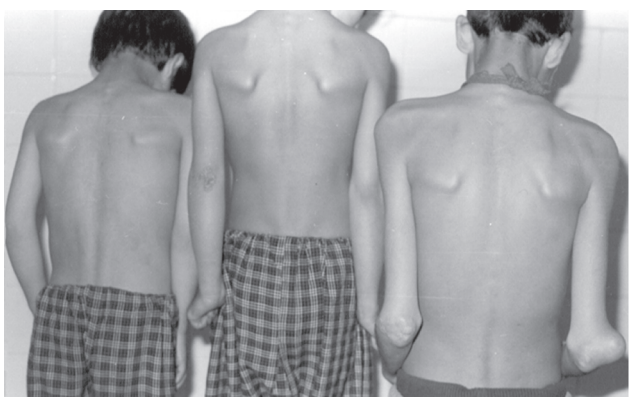

Figure 2 - Siblings of the index case with xanthomas.

Table 1 - Lipidograms of the patient and his siblings.

Name	Age (years)	Cholesterol (mg/dl)	Triglycerides (mg/dl)	LDL-CH (mg/dl)	VLDL-c (mg/dl)	HDL-CH (mg/dl)
Index patient	14	442	175	345	37	60
Sister	9	380	121	308	24	48
Brother	6	387	110	323	22	42
Sister	1.5	209	107	159	21	29
Mother	45	348	276	248	55	45
Father	50	240	80	175	16	49

LDL-CH - low density lipoprotein-cholesterol, HDL-CH - high density lipoprotein-cholesterol, VLDL-c - very low density lipoprotein cholesterol

of receptor precursors from the endoplasmic reticulum to the cell surface; 3. impairment of receptor binding to the ligand; 4. impaired internalization of the receptor–ligand complex due to defective clustering of LDL receptors into coated pits; and (5) defective receptor recycling.[1] Each functional class is associated with mutations in regions of the gene that encode one specific domain of the receptor protein.

Heterozygotes of the FH state respond modestly to a combination of anion exchange resins with a hydoxy-methyl-glutaryl coenzyme A reductase inhibitor. Homozygotes usually do not show much response to medical therapy and generally require selective LDL pheresis, portocaval shunting and liver transplantation.[7,13] However, the report of rigorous cholesterol lowering showed a satisfying clinical response, resulting in prevention of any coronary or aortic valve disease and a near total regression of the xanthomas.[7]

The siblings of our patient have also been put on cholesterol lowering atorvastatin therapy but have not been able to afford the high cost of therapy on a regular basis.

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