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Familial Hypercholesterolemia (Type 2a) in a 6-Year-Old: A Case Study

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Abstract

Familial hypercholesterolemia (FH) is a form of primary hyperlipoproteinemia. FH is a genetic disorder characterized by elevated serum LDL (low-density lipoprotein) levels. Elevated LDL levels are associated with premature atherosclerosis, premature cardiovascular diseases (CVD), and the presence of xanthomas. Homozygous FH is a rare condition with 1 in 1 million occurrences in the general population. For the prevention of premature CVD early diagnosis and treatment is of paramount importance. Statins are the mainstay of treatment with newer lipid-lowering therapies like (PCSK9) inhibitors, and ezetimibe being utilized to treat the condition. Today we discuss a case of a 6-year-old boy presenting with FH with supra-valvular aortic stenosis and xanthomas.

Keywords: Familial Hypercholesterolemia; Low-density Lipoprotein; Cardiovascular Diseases; Cholesterol; Aortic Stenosis

Introduction

Familial Hypercholesterolemia (FH) is a group of genetic disorders that leads to elevated serum total cholesterol and serum LDL cholesterol levels [1]. FH has

- Autosomal dominant and
- Codominant inheritance.

Of these two, autosomal dominant inheritance is more common. The autosomal dominant pattern has two inheritance variants, homozygous and heterozygous. The homozygous variant is rare with fatal risk before 20 years. In the Frederickson classification, FH is classified as 2a, 2b, and 3, with type 2a being the most common type [2]. Highly elevated serum LDL levels are associated with premature CVD. Atherosclerotic changes in the arterial system can be prevented and reversed in the early stages with treatment. FH is the first genetic condition to be recognized to cause myocardial infarction [3]. Skin manifestations commonly present as yellowish skin plaques, skin xanthomas, tendon xanthomas, and xanthelasma [4]. Early detection of FH and aggressive management help in preventing or slowing the progression of premature CVD. First-degree relatives of FH should be screened to identify and treat gene carriers.

Case Report

A 6-year-old male child with a known case of mild aortic stenosis presented with facial puffiness and fast breathing.

Birth history: Born through full-term normal vaginal delivery to the 3rd-degree consanguineous couple, 3rd in birth order, cried immediately after birth, and had no perinatal complication.

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Family history: Mother has multiple small (largest being 2×3cms) lipomas in their forearm and arms. No history of xanthomas in elder siblings and other members of the family. No history of cardiac abnormalities in the family. Mother and father's lipid profiles showed elevated total cholesterol and LDL levels.

History: Full-term male baby delivered through normal delivery, cried immediately after birth with no perinatal complications. The patient was found to have a septal defect on 3rd day of life as he was evaluated and given persistent tachycardia. The patient was managed conservatively and was on regular follow-up. At 2 years of age, given the persistence of visible palpitations which were exacerbated with fever and exertion, a repeat 2D echo was done which showed supra-valvular aortic stenosis with mild left ventricular hypertrophy. The patient was on regular follow-ups since then, asymptomatic with medical management. At 6 years of age, the patient presented with complaints of swelling of the face, vomiting, and visible palpitations, examination suggested features of congestive cardiac failure i.e., raised jugular venous pressure (JVP) and low pulse volume. Echo showed dilated left atrium/left ventricle (LA/LV), non-compaction of LV, severe biventricular dysfunction, mild mitral regurgitation/ mild tricuspid regurgitation. History also revealed recent onset xanthomas over the umbilical region and gluteal regiGivenw of supra-valvular AS, LV dysfunction, and xanthomas congenital hypercholesterolemia was suspected and lipid profile was sent. Lipid profile revealed: LDL - 477, cholesterol - 535, triglycerides - 124, and cholesterol/HDL - 21.9. The patient was diagnosed with FH type-2a and was started on oral atorvastatin, cardivas, minilactone, and ecospirin in appropriate dosages. After a follow-up for 2 months lipid profile showed elevated LDL cholesterol levels with normal triglycerides. Patient was started on evolocumab. Patient received 3 doses of evolocumab with improved skin xanthomas, asymptomatic with persistent LV dysfunction (EF: 26%). Lipid profile showed: cholesterol - 453, triglycerides - 95, HDL - 28, LDL - 406, and cholesterol/HDL - 16.2.

Examination: Patient was conscious, coherent, and oriented to time, place, and person. Higher mental functions were intact.

Height: 109 cm, weight: 13.8 kg, BMI: 11.6 kg/m^2. Head to toe examination revealed eyes: bilateral corneal arcus and developing xanthelasma. Furthermore, bilateral xanthomas over knee, gluteal region, and umbilical region were observed (Figure 1).

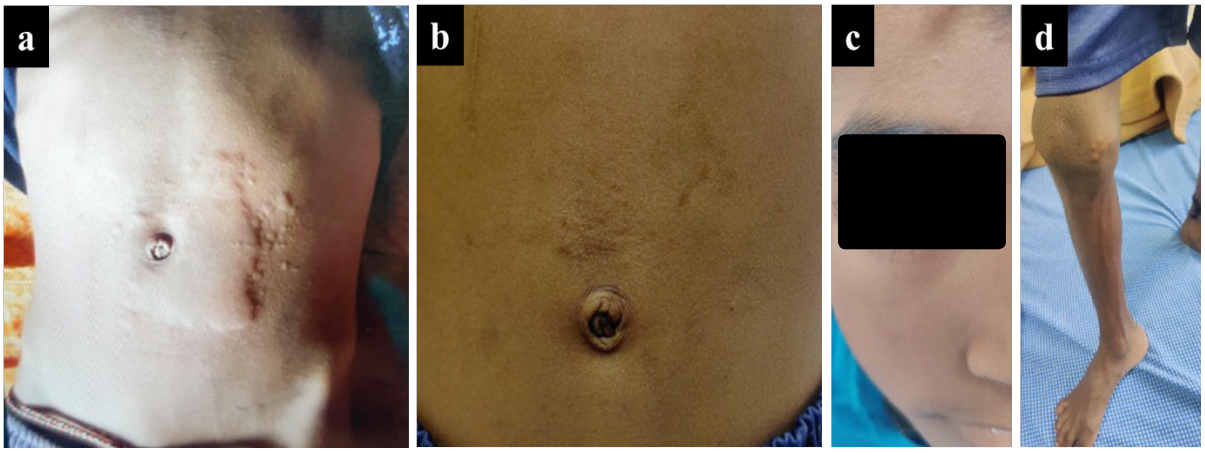

Figure 1: Xanthomas over (a and b) umbilical region, (c) corneal arcus, and (d) knee.

Cardiovascular system examination: Xanthoma over sternum. precordial impulses were seen. Apical impulse seen in palpation: JVP elevated. Parasternal heave present, apical impulse palpated at percussion: auscultation: s1, s2 heard, and ESM present.

- Respiratory system examination: Normal
- Gastrointestinal system: Hepatomegaly present.
- Musculoskeletal: lumbar lordosis and scoliosis present.
- Central nervous system: Normal.

Progression: Xanthomas resolved with medications after oral statins and IV evolocumab.

Treatment approach: Initially thepatient was treated for aortic stenosis. Later on, after hypercholesterolemia was detected, he was started on oral statins, followed by IV evolocumab. Later on, as there was LV dysfunction child was admitted multiple times requiring IV diuretic and inotropic supports. The patient is on continuous diuretics infusion in view of severe LV dysfunction with restricted fluid intake oral diuretics, beta-blockers, and central vasodilators.

Discussion

FH is a type of hyperlipoproteinemia. Hyperlipoprotenemia is classified into primary and secondary hyperlipoprotenemia. Friedrickson classification classifies primary lipoproteinmeinas into 5 types. Of the Frederickson classification, FH comes under type 2a. FH is most common autosomal dominant disorder and rarely autosomal recessive. FH is characterized by high serum LDL cholesterol levels, atherosclerosis, and premature CVD. FH is classified into heterozygous and homozygous variants; homozygous variant has a grave prognosis within the first 20 years of life. The autosomal variant of FH is caused by mutations in three genes,

- LDL receptor,
- Apob gene, and
- PCSK9 gene.

Rarely autosomal recessive disorder involves hypercholesterolemia adaptor protein. LDL receptor mutations account for 85-90% of FH [5]. PCSK9 gene mutations are gain of function mutations and account for less than 5% of FH [6].

In FH, the circulating half-life of LDL cholesterol is nearly doubled to 4.5 days, which leads to marked elevation of serum LDL levels. This excess LDL cholesterol is taken up mainly by macrophages and from foam cells. Adults of age 20 and above should be screened for FH when LDL >190 mg/dl or non-HDL cholesterol >220 mg/dl. Children below 20 years of age must be screened for FH when LDL cholesterol >160 mg/dl or non-HDL cholesterol >190 mg/dl. Tendo xanthomas and xanthelesmas, arcus cornea when present in a patient should prompt the physician to rule out FH. Dutch lipid clinic network diagnostic criteria will be used to diagnose FH [7]. Dutch lipid clinic criteria categorise the patient as definite, probable, possible or unlikely FH based on the interpretation of the criteria.

Medical therapy varies between homozygous and heterozygous FH, because heterozygous FH has at least one functional copy of LDL receptor gene for the statins to work. The initial drug of choice for heterozygous FH is high dose statin. When monotherapy with statins is ineffective, combination therapy with other drugs like ezetimibe can be considered. Bile acid sequestrants can also be added to statin monotherapy. PCSK9 inhibitors are the latest drugs approved to treat FH [8]. Homozygous FH needs prompt diet and lipid lowering therapy [9]. Homozygous FH needs high amount of bile acid sequestrants. LDL apheresis is needed in homozygous FH when diagnosed at age of <5 years. Liver transplant may be the last resort for homozygous FH.

In conclusion, FH is a grave disorder with early mortality due to premature CVD. Early diagnosis of FH plays a critical role in managing the consequences of later life. Early lifestyle changes with lipid lowering therapies help improve the condition of the patient. The past few decades have improved the chances for survival in patients with FH, but a large number of children do not attain the cholesterol levels. There is need for an effective screening strategy and early initiation of lipid lowering therapy to reduce the premature CVD.

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