FAMILIAL HYPERCHOLESTEROLAEMIA- REPORT OF A FAMILY

Venkatesh R. Giri¹, Pranit Farande², S. N. Petkar³, Ajit Barve⁴, Rikita Patel⁵

¹Assistant Professor, Department of Paediatrics, Terna Medical College, Nerul, Navi Mumbai, Maharashtra.

²Assistant Professor, Department of Dermatology and Venereology, Terna Medical College, Nerul, Navi Mumbai, Maharashtra.

³Professor and HOD, Department of Dermatology and Venereology, Terna Medical College, Nerul, Navi Mumbai, Maharashtra.

⁴Medical Officer, Department of Dermatology and Venereology, NMMC, Vashi, Navi Mumbai, Maharashtra.

⁵Resident, Department of Dermatology and Venereology, Terna Medical College, Nerul, Navi Mumbai, Maharashtra.

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PRESENTATION OF CASE

5 years and 3 years old male siblings presented with the complaints of multiple yellowish lesions over buttocks since 3 months noticed by Children's mother. First, they presented in paediatric OPD. After that, patients were referred to Dermatology OPD. On examination there were yellowish, firm, rubbery nodules present on both buttocks. Lesions gradually increased in number and size. There was a history of consanguinity (Third degree), but no family history of acute myocardial infarction, stroke, dyslipidaemia or xanthomas.

The developmental milestones were normal for both the children. There was no history of chest pain, breathlessness, hypertension, diabetes mellitus or hypothyroidism.

DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of cutaneous xanthomas and juvenile xanthogranuloma were kept.

CLINICAL DIAGNOSIS

Based on clinical features, we wanted to rule out cutaneous xanthomas due to familial hypercholesterolaemia.

PATHOLOGICAL DISCUSSION

Both patients were investigated.

(mg/dL)	Sibling 1 (5 years)	Sibling 2 (3 years)
Total Cholesterol	717	735
TG	130	136
LDL	545	590
HDL	89	75
VLDL	20	25

Table 1

(CBC) Liver enzymes, renal functions, blood glucose and uric acid reports were normal. (ECG) and Echocardiography were normal. Plasma cholesterol levels of child's parents were also raised as father's 400 mg/dL and mother's 390 mg/dL. The biopsy of skin showed flattened epidermis, evidence of foamy macrophages seen all throughout the dermis and adipocytes seen interspersed in between them. The findings were consistent with xanthoma.

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Corresponding Author:

Dr. Venkatesh R. Giri,

Shree Balaji Hospital,

Balaai Road, Uran, Navi Mumbai-400702.

E-mail: venkigiri4@gmail.com

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DISCUSSION OF MANAGEMENT

In 1939, FH was first described by Muller.¹ Over thirty years later, Myant² first documented his theory that increased serum cholesterol was due to an increase in LDL particles. Soon thereafter, Goldstein et al recognised that FH was a genetically determined defect within hepatocytes.³ Specifically, he found that the LDL-receptor precursor was not transported to the cell surface in patients with FH; therefore, the LDL-receptors were incapable to bind LDL resulting in an extraordinary elevation in serum LDL.³ Simon Broome formed criteria for definite and possible diagnosis of FH.

Definite Familial Hypercholesterolaemia is defined as-

1. Cholesterol > 6.7 mmol/L [260 mg/dL] or LDL cholesterol > 4 mmol/L [155 mg/dL] in a child < 16 years or total cholesterol concentrations > 7.5 mmol/L [290 mg/dL] or LDL cholesterol > 4.9 mmol/L [190 mg/dL] in an adult, PLUS
2. Tendon xanthoma in the patient or evidence of these signs in first- or second-degree relative, OR
3. DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100 or a PCSK9 mutation.

Possible Familial Hypercholesterolaemia is defined as-

1. Criteria 1 plus 1 of 5 or 6.
2. Family history of myocardial infarction: Below age of 50 in second-degree relative or below age of 60 in first-degree relative.
3. Family history of raised cholesterols- > 7.5 mmol/L [290 mg/dL] in adult 1st or 2nd degree relative or > 6.7 mmol/L [260 mg/dL] in child or sibling under 16.⁴

The Diagnosis of Homozygous FH in our Patient was based on the Presence of-

1. Serum cholesterol levels [Sibling 1 - 717 mg/dL, Sibling 2 - 735 mg/dL] with normal triglyceride levels.
2. Appearance of xanthomas in the first decade of life.
3. Hypercholesterolaemia in both parents.

Familial hypercholesterolaemia is an autosomal dominant genetic disorder. It is caused by a defect on chromosome 19. It may be heterozygous or homozygous variety.⁵ Homozygous FH is clinically characterised by cutaneous xanthomas, enlarged Achilles tendons, atherosclerosis and corneal arcus, usually developing from early childhood. Tendinous xanthoma is asymptomatic, slowly enlarging subcutaneous nodules attached to tendons, ligaments, fascia and

periosteum with normal overlying skin. Extensor tendons of hands, feet and Achilles tendons are involved more frequently. They are often found in association with severe hypercholesterolaemia and elevated LDL level (Fredrickson type 2) and occasionally in hypercholesterolaemia associated with prolonged cholestasis.^{6,7} Some patients with homozygous FH do not have cutaneous xanthomas but acquire tuberous or tendon xanthomas on the elbows, knees or Achilles tendons as older children or adolescents.⁸ The absence of xanthomas in children does not exclude the diagnosis. Arcus cornea may be present to some degree. Total cholesterol levels are usually > 500 mg/dL and can be as high as 1,200 mg/dL.

The prevalence of heterozygotes is 1 in 500 in populations. Although, plasma cholesterol level is increased 2- to 3-fold since birth, but they became symptomatic in 3rd-6th decade of life with tendon xanthoma and cardiovascular complications.⁵ The major complication of homozygous FH is accelerated atherosclerosis, which can result in clinical sequelae even in childhood. Homozygous FH children often have symptoms of vascular disease before puberty, but symptoms can be atypical or go unreported. Sudden death is common.

A child with relatively normal triglycerides and a total cholesterol level > 500 mg/dL with or without cutaneous or tendon xanthomas should be suspected of having homozygous FH. Parents and other relatives should be screened for hypercholesterolaemia. Obstructive liver disease and nephrotic syndrome should be excluded.⁸

Management of FH patients, especially homozygous is challenging. Genetic counselling of the family is of utmost importance. Therapeutic measures include diet modification and drugs such as statins used alone or in combination with bile acid sequestrant, fibrates and Ezetimibe.⁹ LDL apheresis and orthotopic liver transplantation are other available alternatives.¹⁰

Both patients and the family were advised low cholesterol and high-fibre diet. Patients referred to Paediatric Department and were started on Atorvastatin 20 mg/day (3-year-old child) 30 mg/dL (5-year-old child). Parents were referred to Medicine Department for evaluation and management.

Figure 1. Image showing Xanthoma on Buttocks (5 yrs. old Male Child)

Figure 2. Image showing Xanthoma on Buttocks (3 yrs. old Male Child)

Figure 3. Image showing Xanthoma on Buttocks

Figure 4

Figure 5

Figure 4 and 5. Image showing HPE of Xanthoma

FINAL DIAGNOSIS

In view of very high LDL levels, early age of onset, high cholesterol levels in parents and histopathological findings, a final diagnosis of cutaneous xanthomas due to Homozygous Familial Hypercholesterolaemia was done in both patients.

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